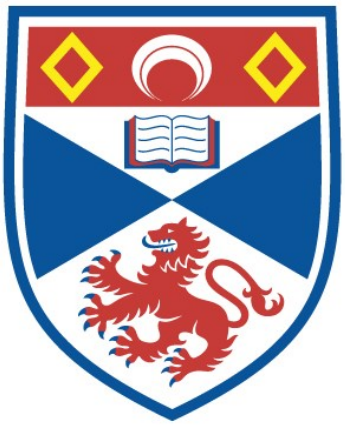
NICKEL- AND PALLADIUM-CATALYSED DEPROTONATIVE CROSS-COUPLINGS

Enrico Marelli

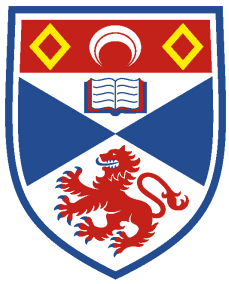
A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



2017

Nickel- and palladium-catalysed deprotonative cross-couplings.

Enrico Marelli



University of
St Andrews

This thesis is submitted in partial fulfilment for the degree of

PhD at the

University of St Andrews

24th May 2017

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Acknowledgements

Firstly, I would like to thank Prof. Steven P. Nolan and Dr. Rebecca J. M. Goss, who gave me the opportunity to pursue my PhD in St Andrews.

Thank you to Prof. Alexandra M. Z. Slawin and Dr David B. Cordes for their help with X-Ray crystallography, and to Prof. Luigi Cavallo and Dr Yuri Minenkov for the computational contribution.

I wish to thank all the colleagues, from both groups, for the invaluable help and the fierce criticisms, the advices, and the enjoyable time spent together. Special thanks go to Dr Martin Corpet, Dr Josè Fernàndez and Dr Sunil Sharma, each of whom closely collaborated with me for a part of the work described in this thesis. Ms Sian Davies, Mr Alessandro Bismuto, Ms Giulia Buccolini, Mr Massimiliano Curcio, Mr Rifahath Mon and Mr Yohann Renault are gratefully acknowledged for the experimental work they provided.

My gratitude also goes to Dr Yusuke Makida, Dr Marcel Brill and Dr Cristina Pubill for the many useful conversations I had with them. Mr Lorenzo Piola, Mr Stefano Guidone, Mr Rik Veenboer, Ms Danila Gasperini, Ms Marie Vasseur and Ms Danai Gkotsi are acknowledged, for being good friends and companions in these 4 years.

Thanks to all the people, inside and outside the School of Chemistry, whose day-by-day presence made these 4 years the great journey they have been. Among them, special thanks go to Anaïs for her loving support.

Last but not least, many thanks to my family: to my mom Lorenza and my dad Leopoldo, to my siblings Tecla and Riccardo, to all my aunts and uncles and grandparents and cousins, present or absent, for believing in me and supporting me this far.

"There is no such thing as problems… only situations"

Guy Ritchie – Revolver

Table of Content

Table of abbreviations

CC: cross coupling
DCC: deprotonative cross coupling
SET: single electron transfer
HTS: high throughput screening
CPME: cyclopentyl-methyl-ether
THF: tetrahydrofuran
DME: dimethoxyethane
DMF: dimethylformamide
DMA: dimethylacetamide
NHC: N-heterocyclic carbene
IMes: 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr: 1,3-bis(2,6-di-isopropyl-phenyl)imidazol-2-ylidene
SIPr: 1,3-Bis-(2,6-diisopropylphenyl)imidazolidinyl-2-ylidene
IPr^{Me}: 1,3-bis(2,6-di-isopropyl-phenyl), 4,5-dimethylimidazol-2-ylidene
IPr*: 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene
IPr*^{OMe}: 1,3-bis(2,6-bis(diphenylmethyl)-4-methoxyphenyl)imidazol-2-ylidene
IPent: 1,3-bis(2,6-di(3-pentyl)phenyl)imidazol-2-ylidene
IHept: 1,3- bis(2,6-di(4-heptyl)phenyl)imidazol-2-ylidene
INon: 1,3-bis[2,6-di(5-nonyl)phenyl]imidazol-2-ylidene
BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Tol-BINAP: 2,2'-bis(di-*o*-tolylphosphino)-1,1'-binaphthyl
Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
NiXantphos: 4,6-bis(diphenylphosphino)-10*H*-phenoxazine
DPPF: 1,1′-ferrocenediyl-bis(diphenylphosphine)
DTPF: 1,1′-ferrocenediyl-bis(di-*o*-tolylphosphine)
D*t*BPF: 1,1′-ferrocenediyl-bis(di-*t*-butylphosphine)
XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
SPhos: 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
Davephos: 2-dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl
Mor-Dalphos: di(1-adamantyl)-2-morpholinophenylphosphine
DTB*n*PP: bis(1,1-dimethylethyl)(2,2-dimethylpropyl)phosphine
D*t*BPB: 2-(di-*t*-butylphosphino)-1,1′-binaphthyl
Zhedaphos: 2-methoxy-6-(N-methyl-N-phenylamino)phenyl(dicyclohexyl)-phosphine
DCyPT: 3,4-bis(dicyclohexylphosphino)thiophene
PEPPSI: pyridine-enhanced precatalyst preparation stabilization and initiation
acac: acetylacetonate
Cp: cyclopentadienyl
cin: cinnamyl
dba: 1,3-dibenzylideneacetone

Am: amyl (1,1-dimethylpropaìyl)
HMDS: hexamethyldisilyazide
OTf: triflate (trifluoromethylsulphonate)
ONf: nonaflate (nonafluorobutylsulphonate)
PLP: (4-formyl-5-hydroxy-6-methylpyridin-3-yl)methyl phosphate, vitamin B6 phosphate

Abstract

Transition metal-catalysed cross coupling chemistry is a valuable tool for synthetic organic chemistry, enabling the preparation of compounds of great interest. The catalytic metal of choice is usually palladium, which generally offer better performances in term of catalytic activity and easy handling. On the other hand, the use of nickel in this class of reactions is gaining attention, as it would provide more economically and environmentally sustainable processes.

Deprotonative cross couplings are a subgroup of these reactions, in which the nucleophile is generated *in situ* by direct deprotonation of a (relatively) acidic C–H bond, for example those of an enolizable ketone or an imine. The reaction products often represent intermediates towards more complex molecular architectures, by virtue of the well-known carbonyl chemistry.

The development of a Pd-catalysed methodology for the prototypical deprotonative coupling, the α-arylation of ketones, is reported in this thesis. It requires significantly lower catalyst loadings compared to previous reports, and displays good tolerance towards functionalised substrates. A related protocol for the intramolecular α-arylation of imines towards indoles was subsequently disclosed: as it requires low catalyst loadings and displays good scalability and simple setup, this methodology is a promising hit for industrial applications.

The parallel development of nickel-catalysed protocols afforded an efficient method for the α-arylation of ketones, using chloroarenes as electrophile for the first time in the literature. The method was further optimised for the synthesis of an intermediate towards a commercial medicinally active compound. Building up on these findings, the first nickel-catalysed protocol for the deprotonative arylation of benzylamine-derived imines was also developed.

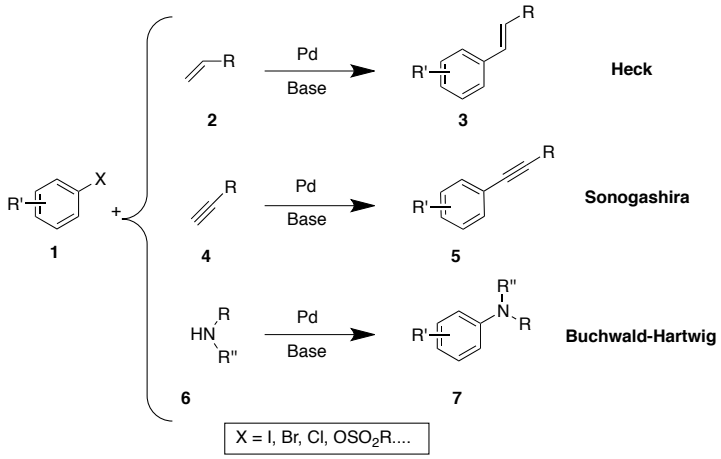
Last, the first aqueous palladium-catalysed protocol for the α-arylation of ketones was investigated. The method proved flexible, showing excellent functional group tolerance: compounds containing base-sensitive functional groups, halogenated small-molecule drugs, and Boc-protected amino acids were all suitable substrates.

1 Introduction

1.1 Modern cross-coupling chemistry and deprotonative cross couplings

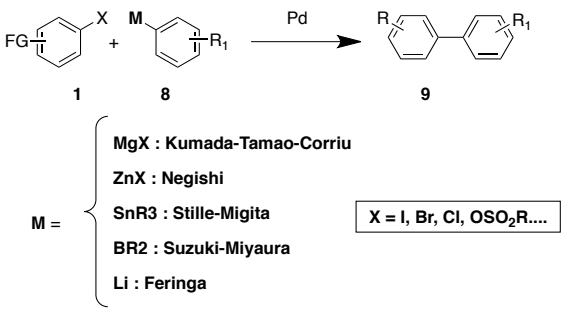
1.1.1 Historical perspective

Metal-catalysed cross-coupling (CC) chemistry undoubtedly represents a milestone achievement for modern synthetic organic chemists, as it allows the straightforward synthesis of a wide range of compounds whose preparation would otherwise be difficult, or even impossible, to accomplish.[1] The access to moieties like 3-arylacrylates **3**, arylalkynes **5** and (poly)arylamines **7** has been made straightforward by the rise of the Pd-catalysed Mizoroki-Heck,[2] Sonogashira[3] and Buchwald-Hartwig[4] reactions, respectively (see **Scheme 1**).



Scheme 1. Examples of Pd-catalysed CCs.

Palladium catalysis also provided access to the biaryl motif **9**, which can today be prepared *via* CC reacting a haloarene with various organometallic reagents. These reactions are now well-known, named after their inventors: Kumada-Tamao-Corriu,[5] Negishi,[6] Stille-Migita,[7] Suzuki-Miyaura,[8] and the coupling of organolithium compounds reported by Feringa in 2013.[9] All these protocols made the diaryl scaffold easily accessible, thus paving the way for the development of many materials and bioactive compounds which contain such motif (see **Scheme 2)**.[10]



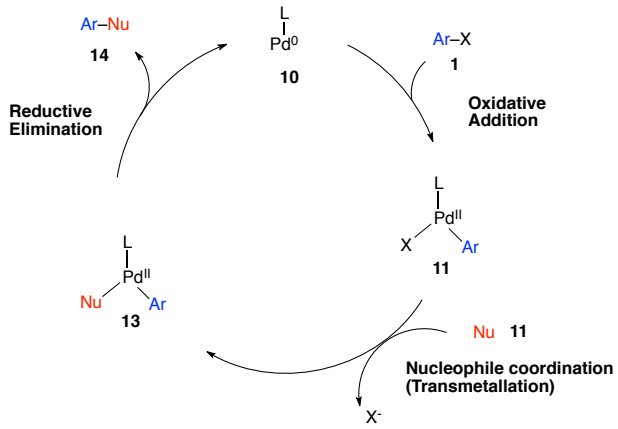
Scheme 2. Synthesis of biaryls using CC chemistry.

Formally, CCs can be considered as reactions between an organic (pseudo)halide electrophile, and a carbon or heteroatom nucleophile, such as organometallic compounds, amines and thiols. A general mechanism for Pd-catalysed cross coupling protocols can be summarised in three key steps:[11]

1) the Pd^0 species **10**, often formed *in situ* by activation of a Pd^{II} source, undergoes an oxidative addition step, activating the C–X bond in the electrophile **1** and thus producing the Pd^{II} species **11**;

2) the nucleophile **12** then coordinates the Pd center in an associative substitution reaction, leading to the dissociation of the halide or pseudo-halide (most commonly, a tosylate or triflate);

3) once both the electrophilic and nucleophilic counterparts are bound to the Pd center in intermediate **13**, a reductive elimination step gives the desired coupled product **14**, regenerating the catalytic Pd^0 species, ready to undergo a new catalytic cycle (see **Scheme 3**).



Scheme 3. Minimal mechanism for Pd-catalysed cross couplings.

It has to be noted that the mechanism of a specific Pd-catalysed CC can involve more steps, depending on the nature of the catalyst and the coupling partners.[1] More

importantly, other catalytic metals can couple these starting materials, through a sometimes intrinsically different mechanism. One paradigmatic example of this difference is the involvement of SET, which has been proved when other metals, especially Fe or Ni are used as catalysts.[12]

The key importance of metal catalysed CC chemistry made it a testing field for organometallic chemists.[13] During the past decades, the efforts have been focused on the understanding of the mechanism of CC reactions, with the following aims:

1) the development of new Pd-catalysed protocols, for example the Buchwald-Hartwig amination, reported in the mid-1990s;[14]

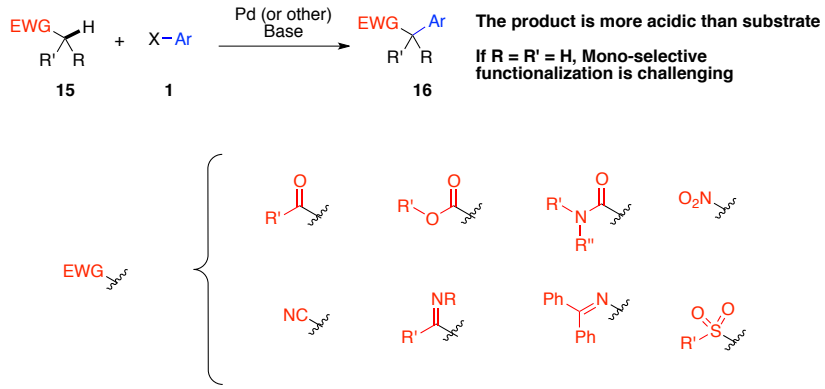
2) the improvement of existing reactions, to such an extent that, for example, the scope of the Suzuki-Miyaura coupling is nowadays remarkably wide, including virtually any kind of functional group;[15]

3) the replacement of Pd catalysts with more earth-abundant and cheaper metals, such as Ni and Cu.[16]

One of the major threads of the research in this area, which enabled many of the aforementioned aims, is the use of ancillary ligands to boost the performance of the catalytic metal(s).[17] Early examples of metal-catalysed CC chemistry relied on the use of ligand-free protocols, often using simple metal sources such as $PdCl_2$, $Pd(OAc)_2$ and $[Ni(COD)_2]$, often with the addition of simple ligands such as PPh_3. Such systems allow the conversion of simple coupling partners, but display important limitations when more challenging reactions are performed. Sterically hindered and/or unactivated substrates, such as chloroarenes or electron-rich bromoarenes, are unsuitable substrates when ligand-free or simpler catalytic systems (*e.g.* triphenylphosphine-supported catalysts) are used. Moreover, the catalytic activity of such systems is usually low, and relatively high catalyst loadings (5 or 10%) are often required.[18] The design of better performing catalysts has led to the study of more sophisticated ancillary ligands, capable of maximising the synthetic potential of metal-catalysed CC chemistry.[17] The following section of this introduction will focus on the development of the class of CC protocols described in this thesis, and will outline the main characteristics that ancillary ligands must display to enable deprotonative cross coupling chemistry.

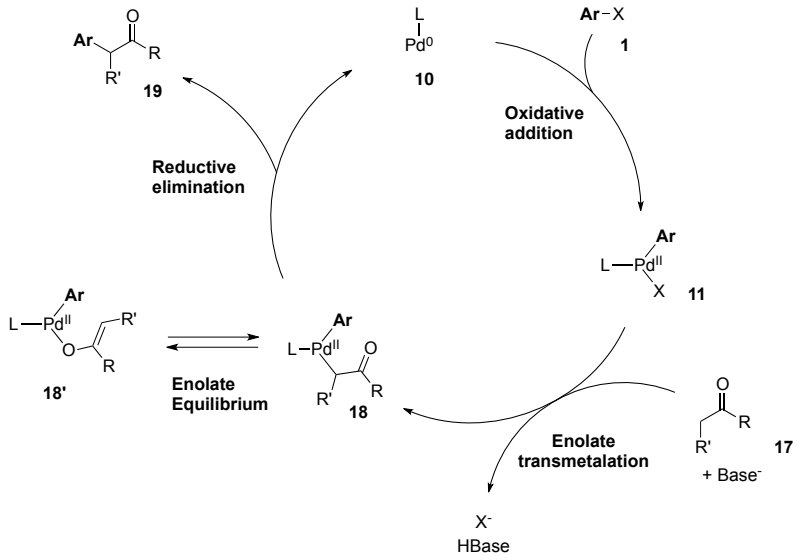
1.1.2 Deprotonative Cross Coupling reactions

As mentioned above, the study of ancillary ligands enabled the disclosure of novel reactivities, *e.g.* the Buchwald-Hartwig amination. Buchwald and Hartwig also contributed, together with Miura, to the development of the Pd-catalysed α-arylation of ketones.[19] This reaction is the first catalytic Deprotonative Cross Coupling (DCC) reported and the basis for the work presented in this thesis. The concept of DCC was introduced by Walsh in 2012.[20]



Scheme 4. The general equation for deprotonative cross coupling processes.

DCC reactions are characterised by the formation of a nucleophilic coupling partner *in situ*, by reaction of a relatively acidic C(sp^3)–H bond and a base. The acidity of the C–H bond is usually due to an electron withdrawing functional group. While carbonyl derivatives (ketones *in primis*) are by far the most studied pro-nucleophiles, arylation α to other electron-withdrawing moieties has been achieved: nitro-, nitrile- and sulphone functional groups all proved to be active in the Pd-catalysed α-arylation reaction. **Scheme 5** shows the typical reaction mechanism of the now well-known α-arylation of ketones as a prototypical example of this kind of processes. The elementary path of a Pd-catalysed cross coupling is followed: the catalytic Pd^0 species activates the C–X bond of the electrophile **1**; the [Pd^{II}(Ar)(X)] **18** complex formed (analogous to complex **11** in **Scheme 3**) can then undergo a transmetalation step with the anionic nucleophile, usually generated by deprotonation of the enolisable ketone pro-nucleophile. the [Pd^{II}(Ar)(enolate)] species **20** undergoes the reductive elimination step, forming the desired C–C bond and regenerating the Pd^0 catalyst.[21]



Scheme 5. Mechanism of the α-arylation of ketones according to Hartwig.[22]

Depending on the nature of the coupling partners, additional relevant steps can be added to the mechanism depicted in **Scheme 3**, leading to more complicated reaction pathways and/or the change in the kinetic behaviour, *e.g.* different rate limiting steps. In the case of the α-arylation of ketones showed in **Scheme 5**, for example, the equilibrium between the C–bound and the O–bound enolates **18** and **18'** is found to be rate-determining, as only **18** can undergo the key reductive elimination step (*vide infra*). Moreover, like in other cases of metal-catalyzed CC processes, this mechanism is not general, especially when using metals other than Pd. The very nature of the reaction pathway can indeed change dramatically: one striking example of this is the study reported in 2014 by Chetcuti and Ritleng on Ni-catalysed α-arylation of ketones (see **Schemes 24 and 25** in this Chapter for further discussion). Nevertheless, some critical features that are common in most of the DCC processes reported so far can be summarised in 5 main points.

1) The arylated product is generally more acidic than the starting material: this often leads to preferential deprotonation of the product, whose conjugate anion can compete with the starting material in the catalytic process, resulting either in formation of polyarylated products, or in slower reactions. The use of an excess of base (2 equivalents or more) is often very beneficial, as it ensures the deprotonation of both substrate and product. This leads to more selective mono-functionalization of the former over the latter, because of its more favourable steric properties.[22] The need for

an excess of base limits the development of asymmetric version of carbonyl arylation, because the newly formed stereocenter is labile to basic conditions, unless quaternary.[23]

2) The selection of the base (more often of the base/solvent system) is crucial, as small differences, for example in solvent polarity or base countercation, can result in dramatic change of reactivity. In some cases, a mild, relatively weak inorganic base (typically Cs_2CO_3 or K_3PO_4) can be used (*vide infra* the monoarylation of acetone), while *t*-butoxides and metal amides are the most common choice for DCCs.

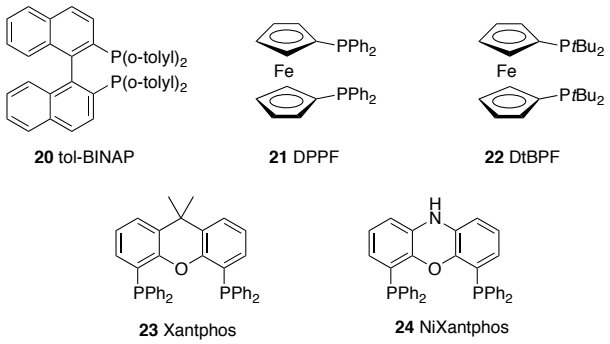
3) The functionalization of a methyl moiety, *e.g.* in an acetophenone derivative, is complicated by the side reactions that it can undergo under the reaction conditions, most importantly self-aldolisation.[22] Moreover, the monoarylated product is highly reactive towards subsequent arylation. The selective monoarylation of such substrates is hence difficult when using non-sterically encumbered, or unactivated aryl electrophiles, even if two equivalents of base are used.

4) In some cases, pre-formation of the anionic nucleophile (*e.g.*, a Zn enolate) or of a synthetic equivalent (*e.g.*, a silylenol ether) is advantageous allowing superior control of the reaction outcome and improves functional group tolerance.[24]

5) Although some examples of ligand-free protocols are known (including the early report by Miura), ancillary ligands play a pivotal role in DCC processes, an importance that has been confirmed by many subsequent studies.[19c,25]

1.1.3 Ligand effect in DCC processes.

Although a wide range of ligands have been tested and proved somehow successful in metal-catalyzed CC chemistry, the introduction of chelating diphosphines (*e.g.* BINAP-, Xantphos- and DPPF-type diphosphines) () has been a major breakthrough in this area during the '90s (see **Scheme 6**).[26] The use of bidentate phosphines was introduced by Hartwig and Buchwald during the development of C–N bond forming catalytic reactions, and substantially improved on the previously reported triaryl-monophosphine-based systems.[27] Bidentate phosphines also represent the "first generation" system for DCC reactions.[28] Some of these systems proved very active: one notable example is the D*t*BPF ligand **22**, initially reported by Hartwig, but subsequently developed by Colacot as one of the most robust ancillary ligand for Pd catalysed α-arylation of carbonyls.[29]

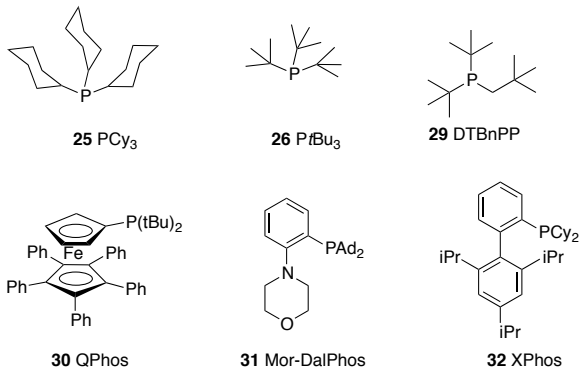


20 tol-BINAP **21** DPPF **22** DtBPF

23 Xantphos **24** NiXantphos

Scheme 6. Examples of bidentate ligands utilised in DCC reactions.

The mechanistic studies on D*t*BPF/Pd catalysed α-arylation led Hartwig to the conclusion that only one of the P atoms of the ligand was bound to Pd through the whole catalytic cycle.[29a] This observation triggered the study of monophosphines as ligands for cross couplings.[30] At the beginning of the 21st century, the development of specifically designed bulky monophosphines, and amine-phosphine bidentate ligands led to significant improvement in CC chemistry (see **Scheme 7)**,[31] and in DCC chemistry especially.[28]

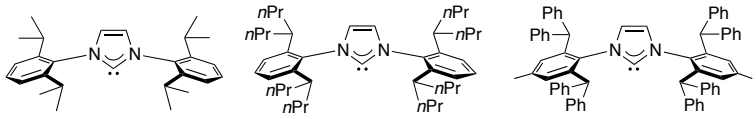


25 PCy_3 **26** P*t*Bu_3 **29** DTBnPP

30 QPhos **31** Mor-DalPhos **32** XPhos

Scheme 7. Selected examples of monodentate phosphines utilised in DCC processes.

Concurrently with these developments, the introduction of N-Heterocyclic Carbenes (NHCs) as ancillary ligands has also provided very efficient methods for the α-arylation of carbonyls and related reactions.[17a] NHCs[32] are carbon-based ligands, whose sterics and electronics are easily tuned by varying the N-substituents and backbone (see **Scheme 8**).[33] Although they have been considered for some time as phosphine *mimics*, studies on their characteristics and behaviour proved that they rather represent an *alternative* to phosphorus-base ancillary ligands, and the applicability of these two classes of ligands sometimes proved complementary.[34]



Scheme 8. Monodentate NHC ligands utilised in DCC processes.

Common traits can be individuated in ligands that promote cross coupling chemistry in efficient way:

1) as mono-ligated Pd species are proved to be the most active in CC chemistry of challenging substrates (*e.g.* chloroarenes), monodentate ligands generally provide superior catalytic activity,[35] with few exceptions,[29,36] because of the high reactivity of the derived, 12-electron species unsaturated [Pd^0(L)] catalytic complex;

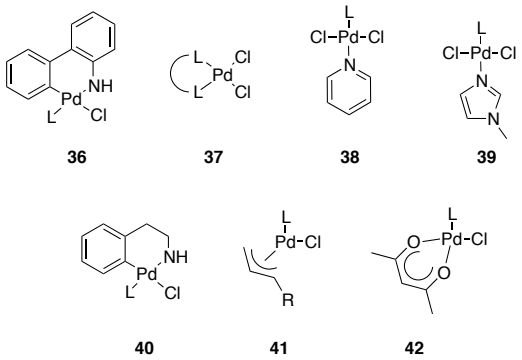
2) the electronic properties of the donor group is crucial, as strong σ-donors (namely, electron-rich) ligands usually give superior activity towards unactivated electrophiles, as they favour higher oxidation state at the Pd center. Moreover, the σ-donor/π-acceptor properties of these ligands also guarantee stronger ligand–metal bond, which limits the catalyst degradation;[37]

3) the steric properties also play an important role, as a crowded environment "protects" the catalytic species (especially in the cases of Pd and Ni catalysed protocols), slowing down the bimolecular decomposition pathway and accelerating the reductive elimination step. The concept of "flexible steric bulk" has been coined,[38] following the observation that rigid bulky substituents around the metal hamper the reactivity, while a more flexible substituent enhances the reactivity;

4) the tunability of the steric and electronic properties allow the design of optimal catalysts in terms of activity and selectivity.[39]

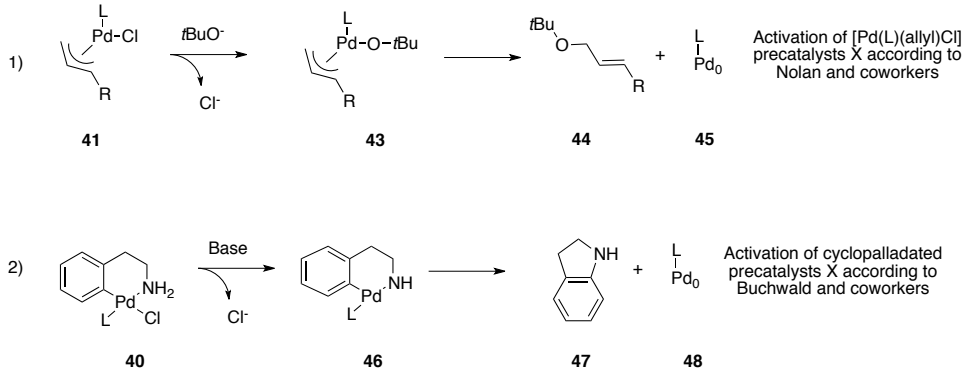
Together with the key importance of the ligand employed, the assembly of the catalytically active complex can also be crucial.[40] The initial results, based on the use of multicomponent catalytic systems, meaning a metal source and a ligand (or a ligand precursor), were subsequently shadowed by the performances displayed by well-defined Pd^{II} pre-catalysts, which often have the additional advantage of being air stable (at least in the case of Pd complexes), and therefore easier to handle. The higher activity has usually been explained by the selective formation of the (putative) active species, avoiding the presence of "unactive" complexes in the reaction mixture.[41]

Studies in this area provided a number of precatalytic architectures in the past 15 years, as outlined in **Scheme 9**.[40]



Scheme 9. Typical architectures of Pd pre-catalysts.

The activation of these well-defined complexes depends on the nature of their structure. The generation of the active Pd^0 species is driven by the reactivity of the so-called "sacrificial" or "throw-away" ligands, usually designed to easily release the catalytic species under the reaction conditions. The mechanism of the activation step is not always unambiguously understood,[42] and different modes of activation are observed for the same pre-catalyst under different conditions.[43] In most cases, however, such step is proven, or at least supposed, to occur by nucleophilic attack on a Pd^{II} centre, followed by reductive elimination generating a $[Pd^0(L)_n]$ species. Complexes **41** (and derivatives), for example, are activated by attack of a *t*-butoxide anion followed by reductive elimination of a product **44**, as shown in **Scheme 10**, equation 1.[43a] In the cases of complexes **40**, the activation proceeds through deprotonation of the amine, followed by reductive elimination to give indoline **47** (**Scheme 10**, equation 2).[44]



Scheme 10. Modes of activation of selected pre-catalyst architecture ("throw-away" ligands).[43,44]

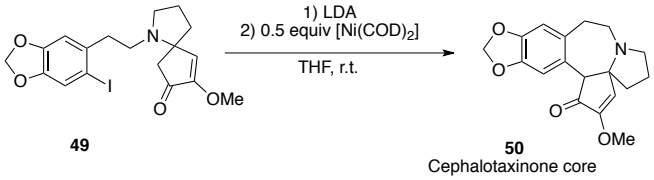
The crucial reports about carbonyl α-arylation reactions of ketones will be summarised in **Section 2** of this introduction, while **Section 3** will focus on the functionalization at

benzylic C–H positions. The application of deprotonative cross couplings to the synthesis of heterocycles will be covered in **Section 4**. It has to be noted that most of these protocols rely on the use of Pd as catalytic metal; nevertheless, important examples of DCCs are reported with other catalysts, especially the cheaper and more widely available first-row transition metals Cu and Ni. Such methodologies will be mentioned in the respective relevant paragraphs, in order to give a most comprehensive overview of all the options available in the synthetic chemist's arsenal.

1.2 α-arylation of ketones

1.2.1 Main examples of α-arylation of ketones

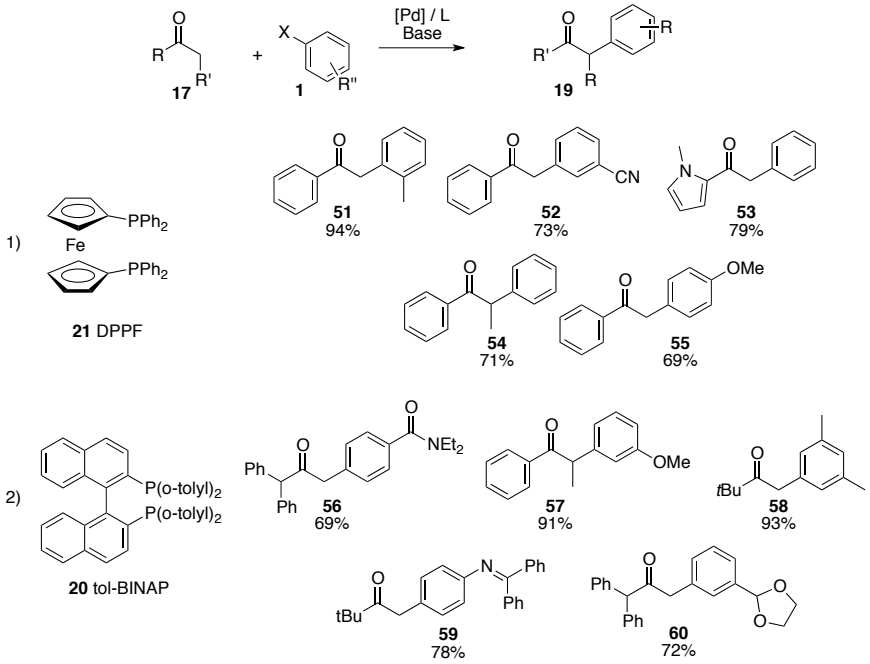
α-aryl carbonyls represent a widespread motif in many bioactive compounds and/or intermediates towards their synthesis. During the past decades, classic organic synthesis has provided a variety of stoichiometric methods for their preparation.[45] Despite their utility, these protocols display many crucial drawbacks, hampering not only their applicability on large scale, but also their generali and easy application on laboratory scale. Indeed, the need for a methodology that easily delivers such scaffolds, led to the first example of metal-mediated α-arylation of a ketone, reported in 1973. Semmelhack used quasi-stoichiometric amounts of Ni for the intramolecular coupling between the enone moiety and the aryl iodide group in compound **49**, leading to the core of the natural product Cephalotaxinone **50** (see **Scheme 11**).[46]



Scheme 11. First example of α-arylation of ketones: the synthesis of Cephalotaxinone according to Semmelhack.[46]

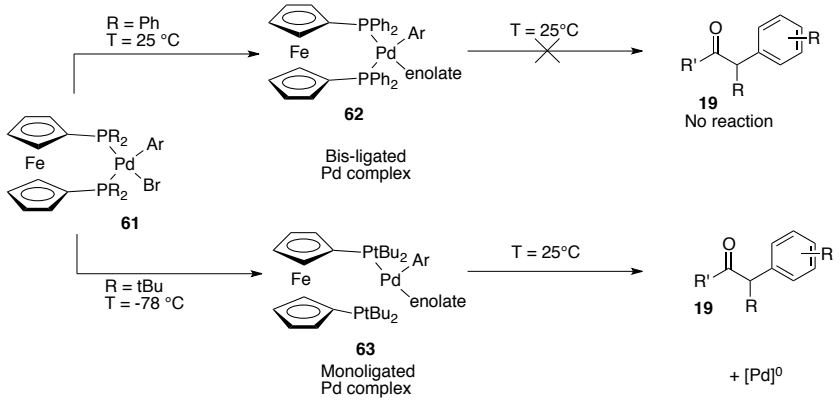
The first Pd-catalysed versions of α-arylation of ketones were reported concurrently by Miura, Buchwald and Hartwig (see **Scheme 12**).[19] The use of a bidentate ancillary ligand (DTPF (**Scheme 12**, equation 1) by Hartwig, Tol-BINAP (**Scheme 12**, equation 2) by Buchwald), together with a Pd source, gave good performances for a range of coupling partners. These initial findings mainly focused on the use of activated iodo-

and bromoarenes. It is noteworthy that these early reports contain examples of acetophenone derivatives as pro-nucleophiles, later found to be challenging substrates.



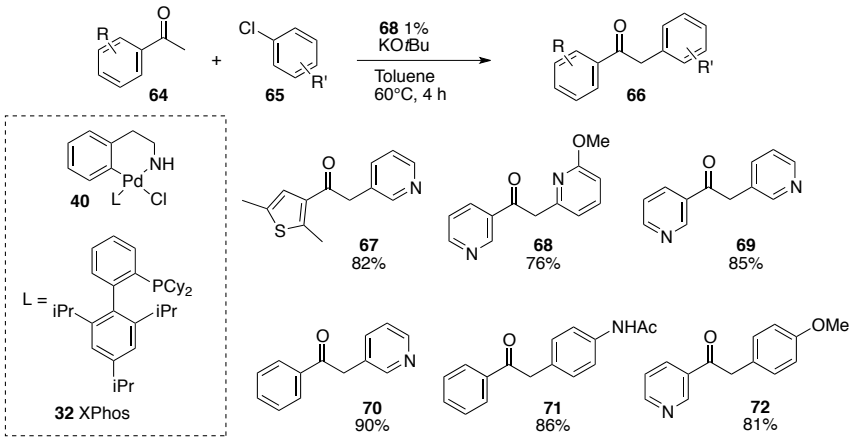
Scheme 12. First general examples of arylation of ketones and selected examples of the scope. 1) Conditions: 7.5 mol% [Pd(dba)$_2$], 9 mol% DTPF, refluxing THF, 2h; b) Conditions: 2.5 mol% [Pd$_2$(dba)$_3$], 6.0 mol% tol-BINAP, 70 °C in THF, until completion. X=Br or I. [19]

Hartwig proved that D*t*BPF ligand gives superior results when compared to other bidentate ligand.[29a] Further studies suggested that such an improved performance could be due to the de-coordination of one of the P donors during the catalytic cycle, because of the large steric bulk and of the electronic properties of this ligand (see **Scheme 13**).



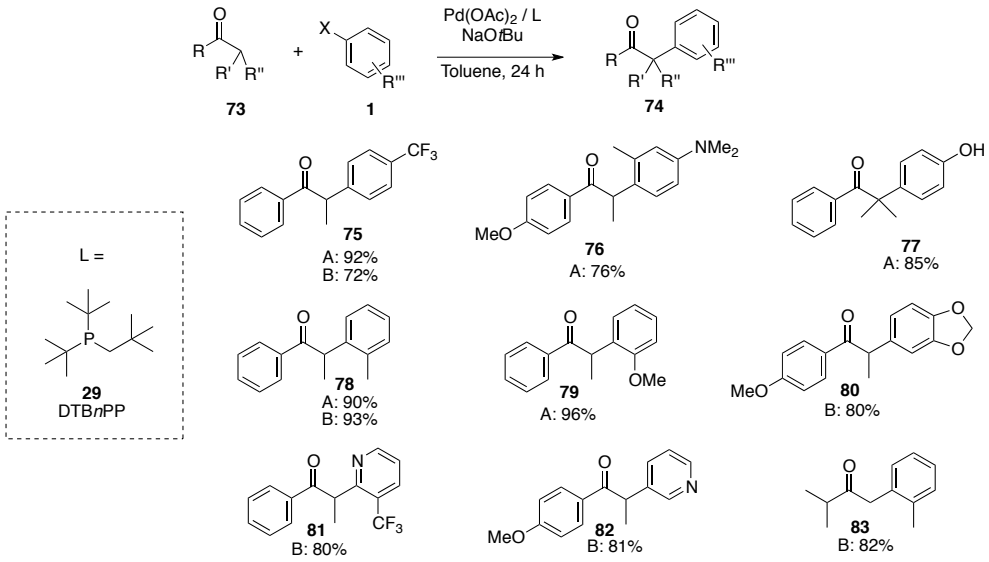
Scheme 13. The mechanism of the reductive elimination from Pd-diphosphine complexes confirms only one P-donor is necessary.[29a]

The above-mentioned studies were crucial to shed light on the mechanism of the reaction (which is shown in **Scheme 5**). Such findings triggered the study of monodentate phosphines to perform this transformation: early studies by Hartwig proved that PCy_3 and $PtBu_3$ were suitable for such transformation, and led to the development of monodentate ligands for CC chemistry.[29a] Other studies involving monodentate phosphines were carried out by Beller and Hartwig, showing the catalytic potential of this class of ligands.[47] Buchwald subsequently proved that very bulky monodentate phosphines, such as XPhos, provide excellent selectivity even when acetophenone derivatives were used.[48] These results confirmed the hypothesis, previously reported by Buchwald, that increased steric bulk can significantly improve the performance of CC catalysts (see **Scheme 14**).[49]



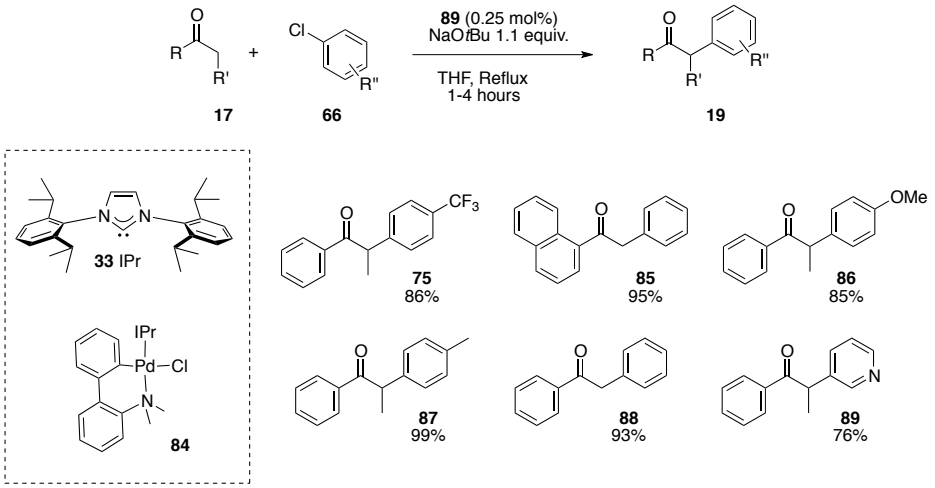
Scheme 14. α-arylation of arylmethylketones using an XPhos-based pre-catalyst according to Buchwald (selected examples, total scope 12 entries).[49]

Despite these exceptional results obtained with monodentate phosphines, it has to be noted that some bidentate ligands, like the aforementioned D*t*BPF **21** and NiXantphos **24**, provided catalytic activities comparable with those achieved with monodentate ligands, and are still used in this (and others) CC reaction. Specifically designed ligands like XPhos are often the most successful ones in α-arylation of ketones, although the use of simpler phosphines is still a field in development, as demonstrated by the protocol reported by Shaughnessy in 2014 (see **Scheme 15**).[50]



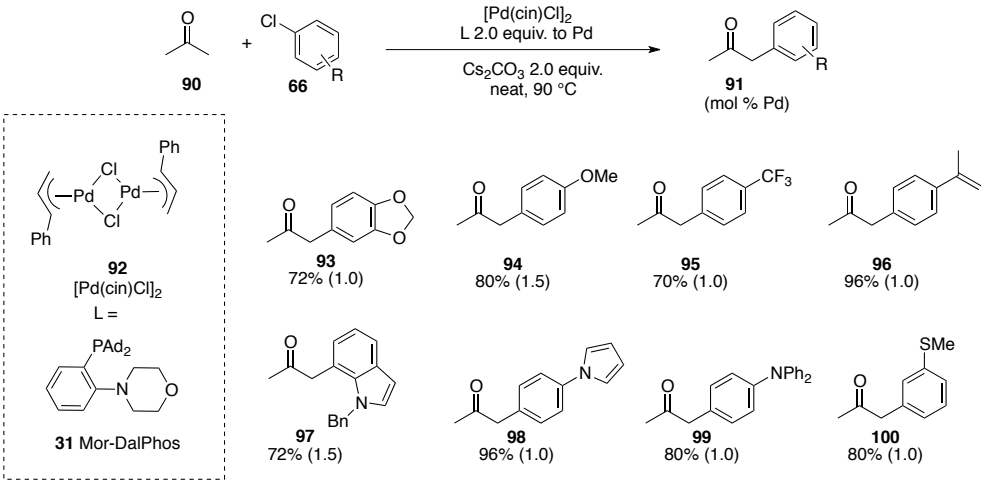
Scheme 15. α-arylation of ketones using DTBNpP ligand according to Shaughnessy (selected examples, total scope 25 entries). Conditions **A:** X=Br, T= 50 °C, [Pd] = [DTBnPP] = 0.25 mol%. Conditions **B:** X=Cl, T = 80 °C, [Pd] = [DTBnPP] = 0.50 mol%.[50]

The success of monodentate phosphines in the α-arylation of ketones prompted the study of other classes of ligands. The application of NHCs in CC chemistry has been pioneered by Nolan, who proved the suitability of their NHC-bearing, Pd-based well-defined pre-catalysts in the α-arylation of ketones.[51] Subsequently, the same group, and others, reported on the use of various classes of well-defined, NHC-containing pre-catalysts for this reaction. **Scheme 16** shows the results reported by the same group 2006. The use of the NHC-based pre-catalyst **89** resulted in high yields of coupled products even at relatively low (0.25 mol%) catalyst loading.[52]



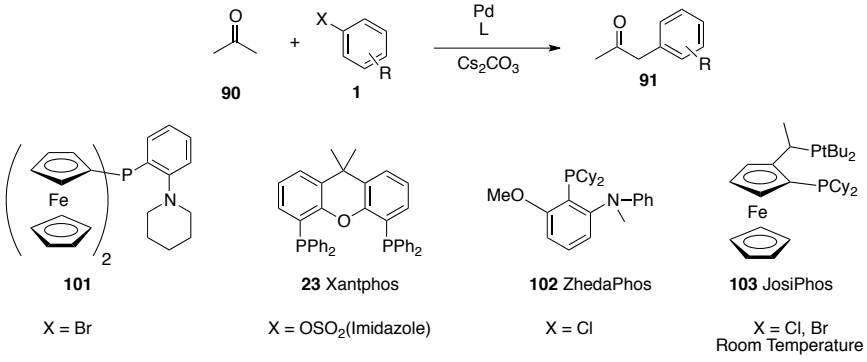
Scheme 16. α-arylation of ketones at low catalyst loading using an NHC-based pre-catalyst according to Nolan (selected examples, total scope 16 entries).[52]

An interesting field that has emerged in this area since 2011 is the selective mono-arylation of acetone. Such a transformation is challenging because of the high reactivity of the mono-arylated products, that hampers the selective monoarylation and the poor reaction rates showed by small ketones, because of the slow reductive elimination step.[53] In 2011, Stradiotto reported the first mono-selective catalyst for acetone arylation, using the P–N ligand Mor-DalPhos **97** (see **Scheme 17**).[54] The protocol shows an impressive scope of chloro- and bromoarenes at catalyst loadings as low as 1 mol%. The same catalytic system has also been successfully applied to α-arylation of more common substrates (aryl- and cyclic ketones),[55] and to carbonylative α-arylation processes.[56]



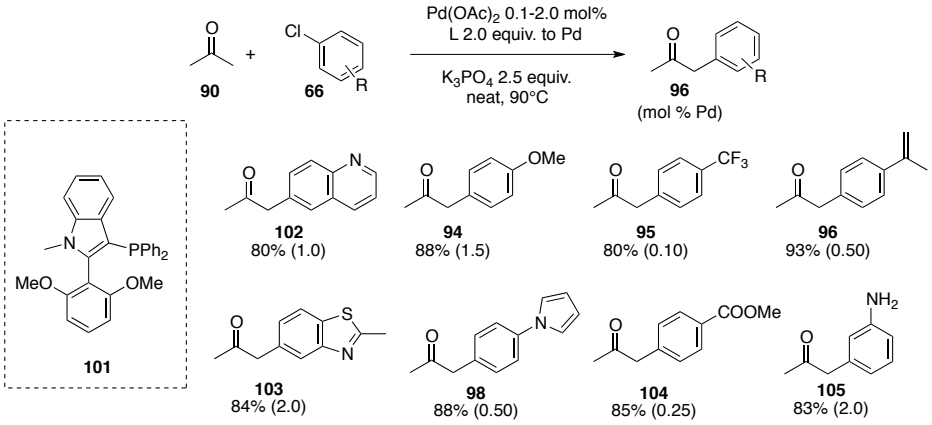
Scheme 17. α-arylation of acetone, according to Stradiotto (selected examples, total scope 21). Catalyst loadings shown in parenthesis.[54]

After the first disclosure, a number of protocols for the α-arylation of acetone were disclosed (see **Scheme 19**), using a wide variety of catalytic systems and aryl electrophiles.[57]



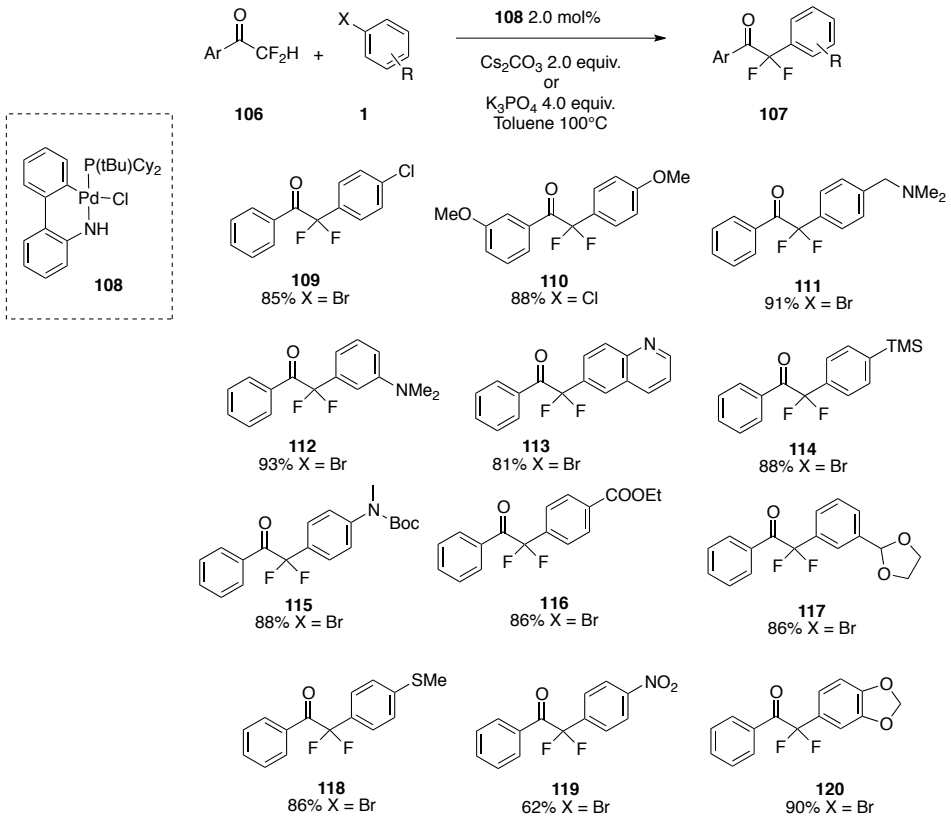
Scheme 18. Other ligands for the α-arylation of acetone.

A recent report by Kwong proved that the specifically designed indolylphosphine **106** provides superior performances in this transformation: the desired mono-arylated products were obtained in good yields with catalyst loading as low as 0.1 mol% in some cases (see **Scheme 19**).[58]



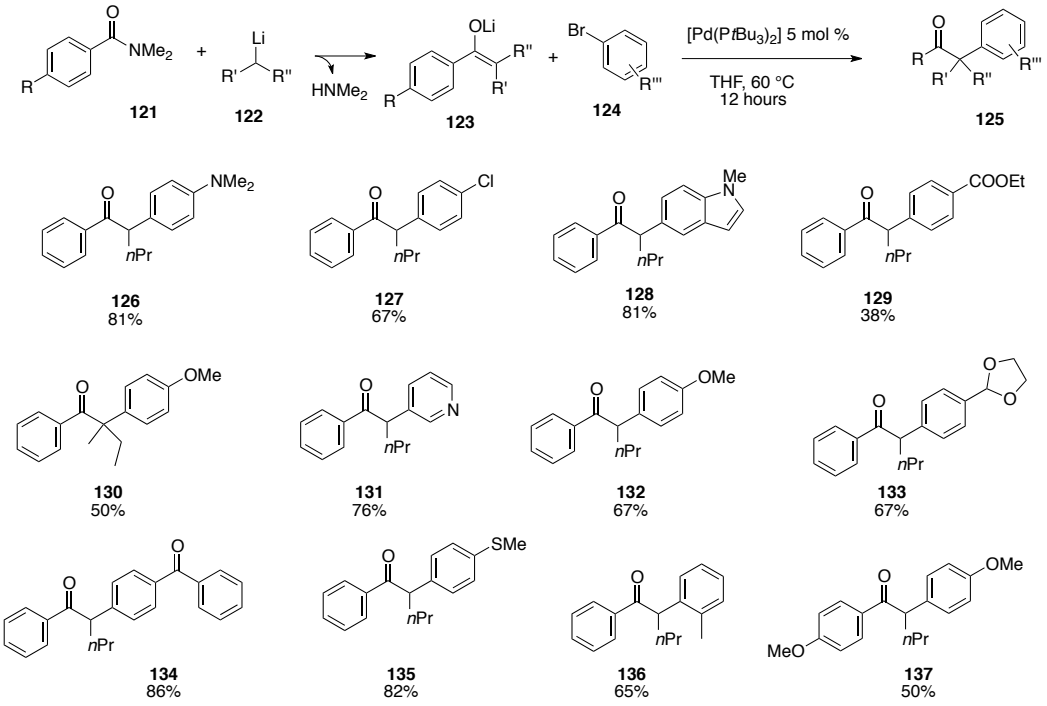
Scheme 19. Specifically designed, high-performance indolylphosphine for the the α-arylation of acetone. (selected examples, total scope 25 entries).[58]

In 2014, the α-arylation of α,α-difluoromethylketones (see **Scheme 20**) was disclosed by Hartwig,[59] who used the well defined phosphine-containing palladacycle **114** as pre-catalyst to accomplish the coupling of these pro-nucleophiles. The reactivity of difluoroketones in cross coupling reactions is limited by their electronic properties, that make the reductive elimination step sluggish. Their utility in the one-pot, two steps synthesis of difluoromethylarenes, which are difficult to obtain by other means, was demonstrated for a wide scope (31 entries), was proven. This methodology highlights the extreme versatility of the α-arylation of ketone in the context of synthetic organic chemistry.



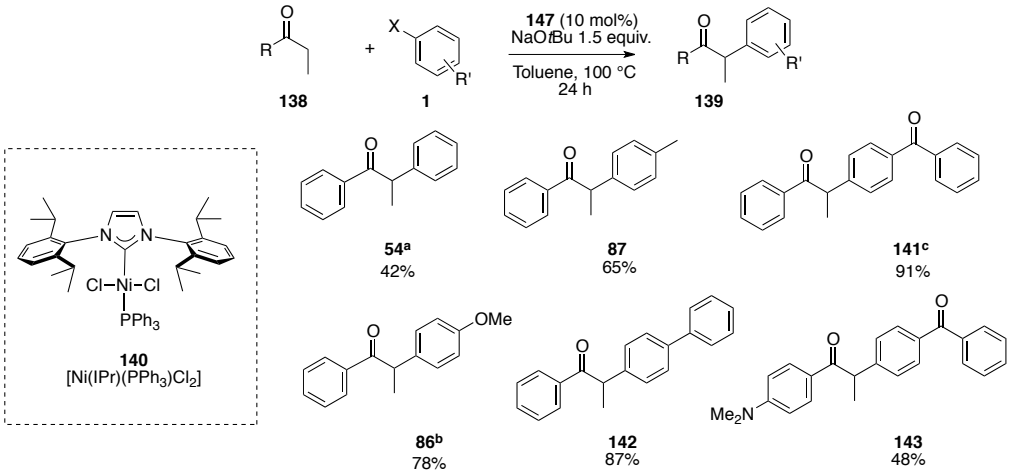
Scheme 20. α-arylation of difluoromethylarylketones according to Hartwig (selected examples, total scope 31 entries).[59]

In 2016, Feringa reported a protocol for the generation of lithium enolates by reacting benzamide derivatives and organolithium reagent. The subsequent α-arylation of the enolates were then achieved one pot, without the use of additional bases. Although the yields ranged from modest to good, this strategy potentially represents an entrance to variously functionalised α-arylketones (see **Scheme 21**).[60]



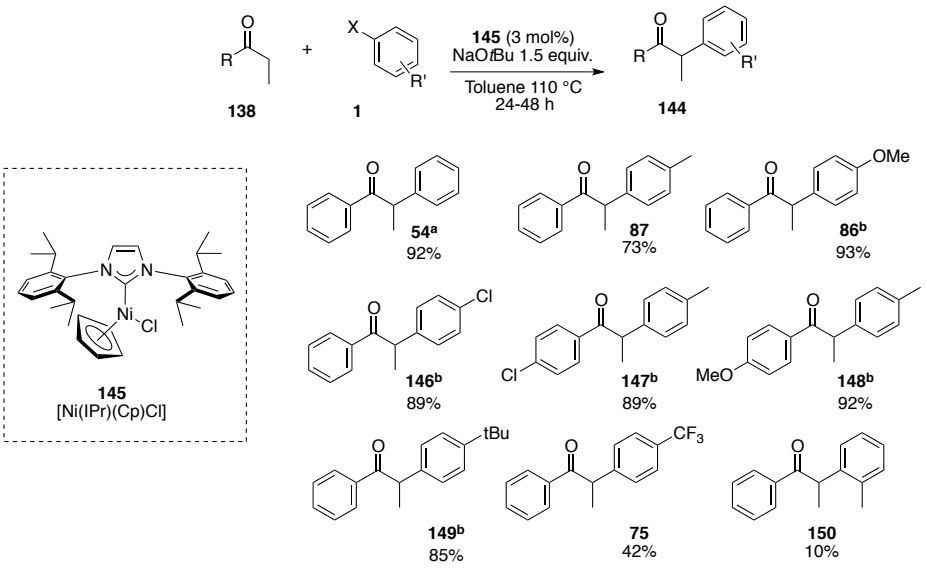
Scheme 21. One pot α-arylation of enolates generated by nucleophilic attack of an organolithium reagent on amides, according to Feringa (selected examples, total scope 22 entries).[60]

As previously mentioned, other metals were used for this transformation. In 2007, the first example of Ni-catalysed α-arylation of ketones was reported by Matsubara using the mixed NHC/phosphine well defined Ni pre-catalyst **140** (see **Scheme 22**).[61] Despite the many drawbacks this method suffered (unsuitability for methyl ketones and unactivated chloroarenes, high catalyst loading, moderate yields), it represented an important milestone for Ni-catalysed cross coupling, which was until then limited to the stereoselective arylation of tertiary, cyclic ketones.[62]



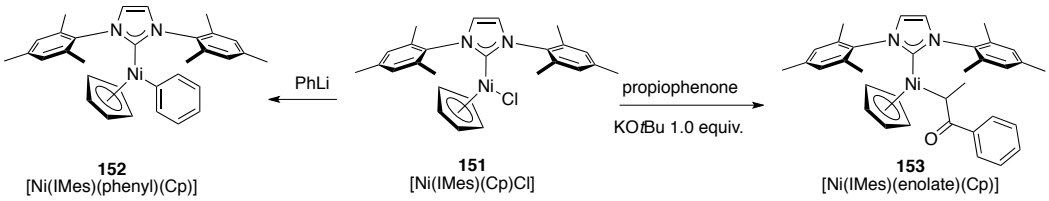
Scheme 22. Ni-catalysed α-arylation of propiophenone derivatives according to Matsubara (selected examples, total scope 11 entries). X= Br unless otherwise specified. [a] X= Br; When X = Cl, 58% yield was obtained. [b] X=Br; when X=Cl, 39% yield (NMR) was obtained. [c] 5 mol% [Ni].[62]

In 2014 Chetcuti and Ritleng reported on the [Ni(NHC)(Cp)Cl]-catalysed α-arylation of ketones (Cp = cyclopentadienyl).[63] When the NHC ligand is IPr (see **Scheme 23**), this system showed improved activity with respect of Matsubara's, allowing the conversion of a range of bromo- and iodoarenes at 3 mol% catalyst loading, obtaining moderate to good yields. However, the use of more challenging substrates, namely methyl ketones and chloroarenes, led to poor or no conversion.



Scheme 23. Ni-catalysed α-arylation of ketones according to Chetcuti, Ritleng (selected examples, total scope 23 entries). Unless otherwise noted, X= Br and t= 24 h. [a] X= I. [b] t= 48 h.[63]

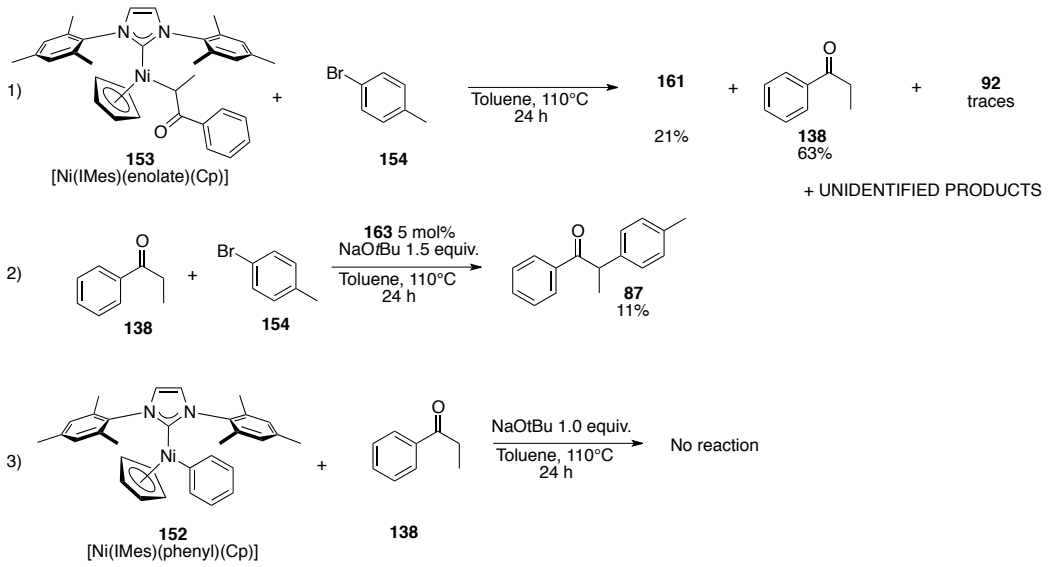
Complexes **152** and **153** were synthesised starting from [Ni(IMes)(Cp)Cl] **151**, with the aim of probing their involvement as catalytic intermediates in the CC reaction (see **Scheme 24**). Complex **151** is a competent catalyst for the reaction, although less efficient than its IPr congener **145**; the synthesis of possible Ni-enolate and Ni-aryl intermediates of this complexes was reported to be difficult, because of the instability of such derivatives.



Scheme 24. Generation of putative reaction intermediates from pre-catalyst **151**, according to Chetcuti and Ritleng.[63]

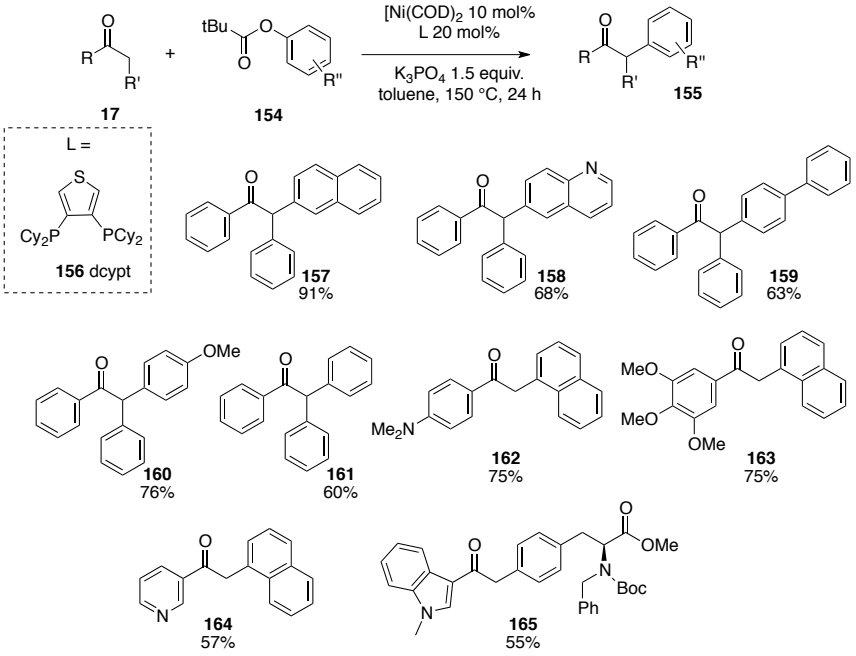
These studies showed that this process does not involve under a Ni^0-Ni^{II} cycle, probably because of the strong ligation of the Cp moiety to the Ni center (see **Scheme**

25). Complexes **154** and **153** failed to provide significant amount of coupled products; a radical mechanism was therefore proposed by the authors. This result proves that the ancillary ligand plays a crucial role in DCCs also in cases when the mechanism is not the "common" one.



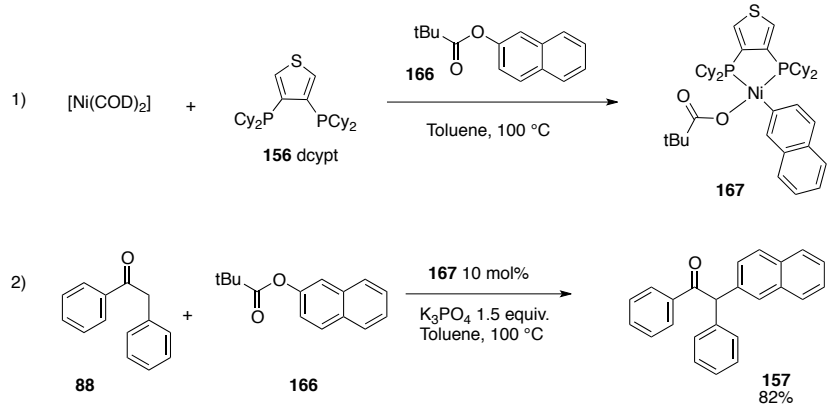
Scheme 25. Mechanistic studies on the [Ni(NHC)(Cp)Cl] class of pre-catalysts according to Chetcuti and Ritleng.[63]

In the same year, Itami and Yamaguchi reported on a Ni-catalysed aryl-pivalate C–O activation/α-arylation of ketones).[64] Despite the high temperature required (150 °C in toluene), this methodology shows a spectacular functional group tolerance, allowing the coupling of a large array of heterocycles and functional groups, including enantiopure aminoacid derivatives. Methyl ketones were tolerated when naphthalene-derived aryl pivalates were used, although moderate yield were observed when less sterically hindered aryl pivalates were used (see **Scheme 26**).



Scheme 26. Ni-catalysed α-arylation of ketones using pivalates as electrophiles according to Itami, Yamaguchi (selected examples, total scope 29 entries).[64]

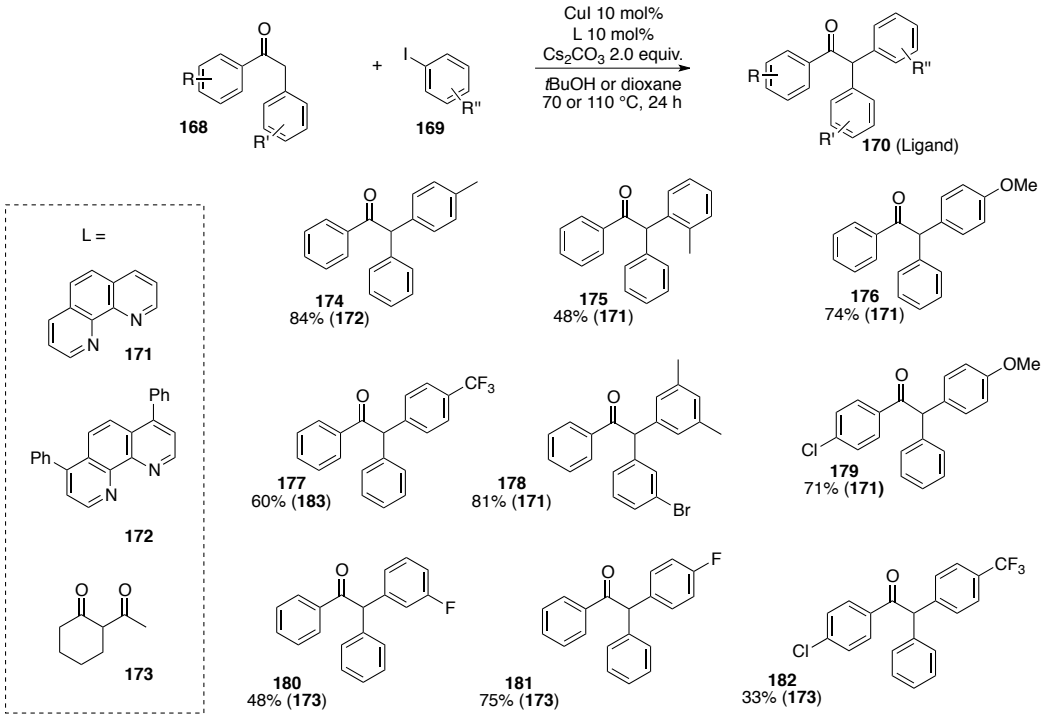
The authors also isolated the intermediate **167** derived from the oxidative addition of the aryl pivalate **166** to the L/Ni^0 complex; this complex was active as a catalyst in the transformation (see **Scheme 27**). This result indicates that a Ni^0-Ni^{II} mechanism is active in this case.



Scheme 27. Mechanistic studies on the mechanism of the Ni-catalysed ketone arylation of ketones according to Itami and Yamaguchi.[64]

Another first row transition metal that proved to be active in the α-arylation is Cu. Copper is commonly used in cross coupling catalysis, especially for arylation of amines and amides. Taillefer reported in 2012 the first example of Cu-catalysed α-arylation of ketones, using ligands **171-173** in junction with CuI as catalyst (see **Scheme 28**).[65] This system is limited to aryl-benzyl ketone derivatives, and shows a limited functional

group tolerance. Nevertheless, its synthetic utility has been proven by employing it in a concise synthesis of Tamoxifen.



Scheme 28. Cu-catalysed α-arylation of deoxybenzoin (arylbenzylketones) according to Taillefer (selected examples, total scope 18 entries).[65]

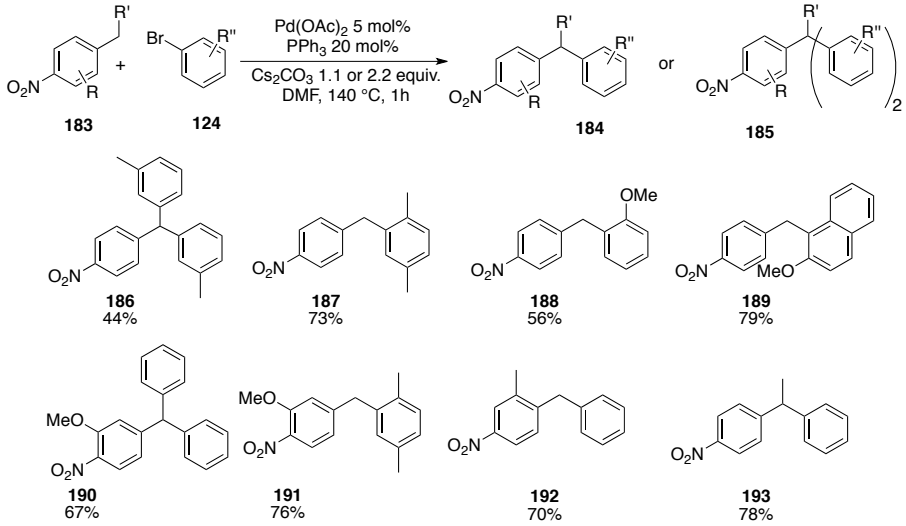
1.3 Deprotonative Cross-Couplings at α-benzylic position

Benzylic C–H bonds notoriously display peculiar reactivity, dictated by the close position of aromatic rings, that increase their acidity and lower their nucleophilicity.[66] Polyarylated benzylic derivatives, such as triarylmethanes and (diarylmethyl)amines have showed interesting properties in many areas, particularly for optoelectronic materials, [67] and in medicinal chemistry (for more information about the (diarylmethyl)amine moiety, see **Chapter 5**). The development of CC protocols towards these motifs potentially provides a simple and general pathway toward these classes of compound.

1.3.1 Arylation of (poly)arylmethanes.

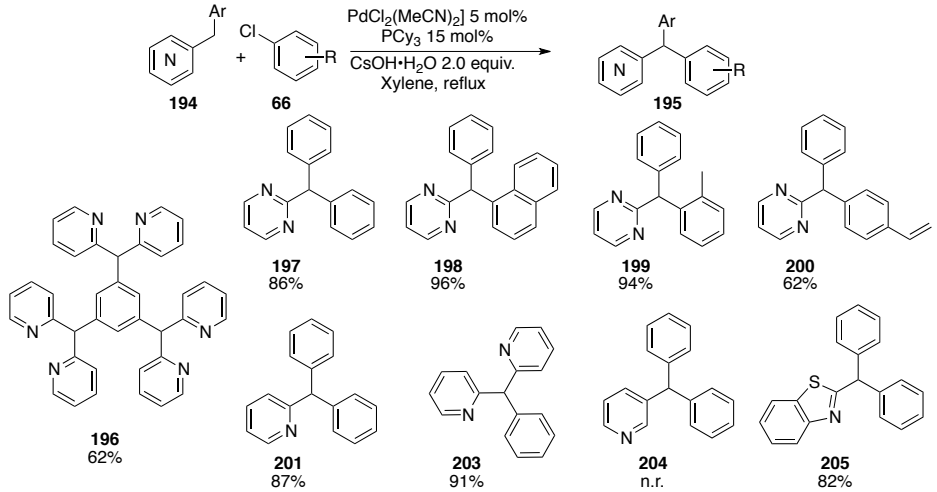
The development of Pd-catalysed DCC chemistry towards the synthesis of polyarylmethanes was pioneered by Miura, who reported the first transition metal-catalysed arylation at the benzylic position of *p*-nitrotoluene derivatives in 1998.[68] The reaction was either mono- or di-selective, depending on the steric properties of the coupling partner; moderate to good yields were observed (see **Scheme 29**). The need

for a strong electron-withdrawing group on the aromatic ring of the pro-nucleophile, together with the high temperature required, limited the scope of this transformation.



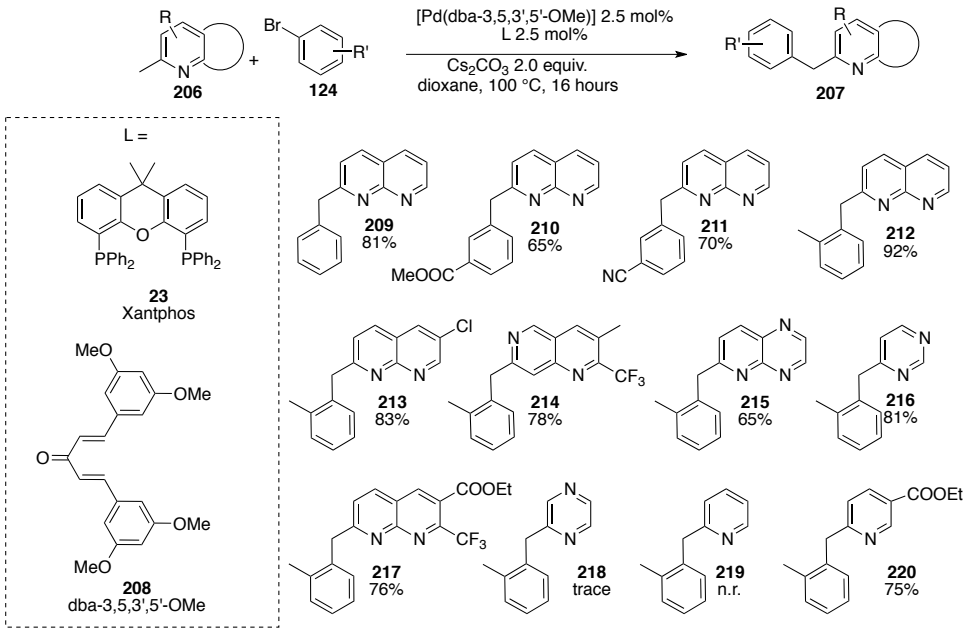
Scheme 29. Arylation of electron-deficient toluene derivatives according to Miura (selected examples, total scope 11 entries).[68]

The group of Yorimitsu and Oshima subsequently reported the first direct arylation of diarylmethanes under Pd catalysis, using $[Pd(MeCN)_2Cl_2]/PCy_3$ as catalyst and $CsOH \bullet H_2O$ as base (see **Scheme 30**).[69] The reaction allows the synthesis of complex compounds, for example the polycoordinating architecture of compound **196**, but the study covered only few haloarenes. The presence of a nitrogen-containing aromatic ring was necessary, but not sufficient, to achieve this transformation: entry **204** shows that a 3-benzylpyridine could not be used as pro-nucleophile.



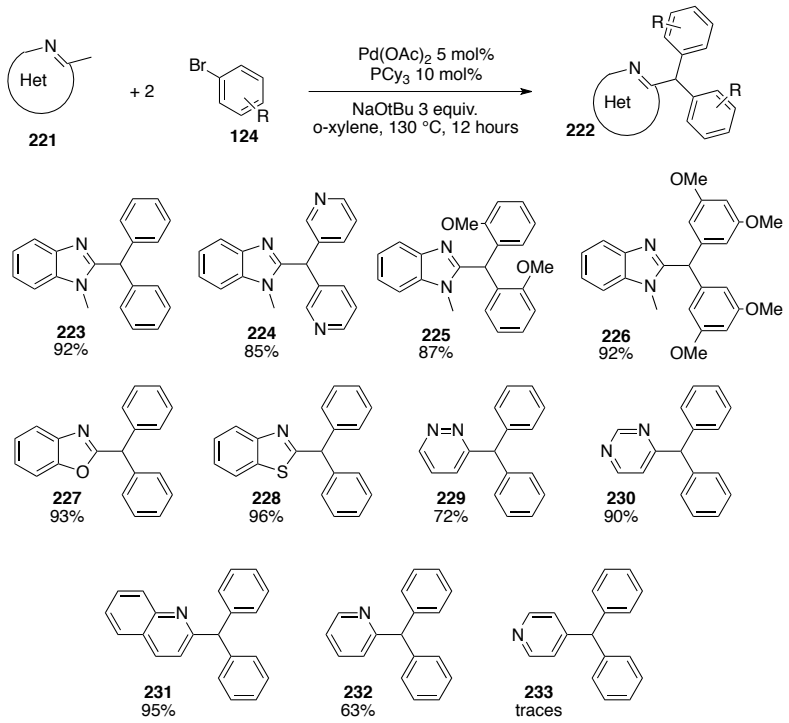
Scheme 30. Benzylic arylation according to Yorimitsu and Oshima (selected examples, total scope 16 entries).[69]

In 2010, Morris and Burton reported the deprotonative Pd catalysed mono-arylation of nitrogen-containing methyl-heterocycles.[70] Their catalytic system was based on Xantphos, while different Pd sources, such as $Pd(OAc)_2$, $Pd_2(dba)_3$ and $(MeCN)_2PdCl_2$ could be used successfully. The authors observed that the best results were obtained when using the Fairlamb catalyst, a tetramethoxydibenzylideneacetone (**208**)-based version of $Pd(dba)_2$ (see **Scheme 31**). A wide scope of naphthiridine, pyperazine, pyridine and quinoline derivatives was synthesised *via* arylation at their benzylic position. The system shows an impressive functional group tolerance, and is appealing for late stage functionalization of such heterocycles (see entry **217**), although also in this case substrate specificity was observed. Bromo- and iodoarenes, as well as aryl triflates, were suitable electrophiles for this transformation, while the use of chloroarenes resulted in no reaction.



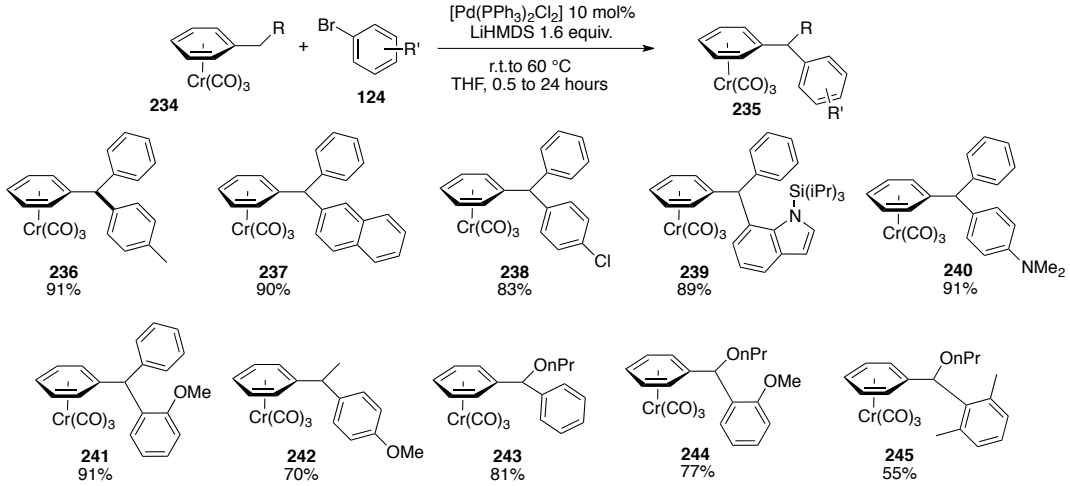
Scheme 31. Benzylic arylation according to Morris and Burton (selected examples, total scope 29 entries).[70]

A similar approach was reported by Li,[71] using $Pd(OAc)_2/PCy_3$ and NaO*t*Bu, for the arylation of (heteroaryl)-CH_3 moieties. In this case, only diarylation products were observed, making the selective synthesis of differently substituted compounds impossible (see **Scheme 32**).



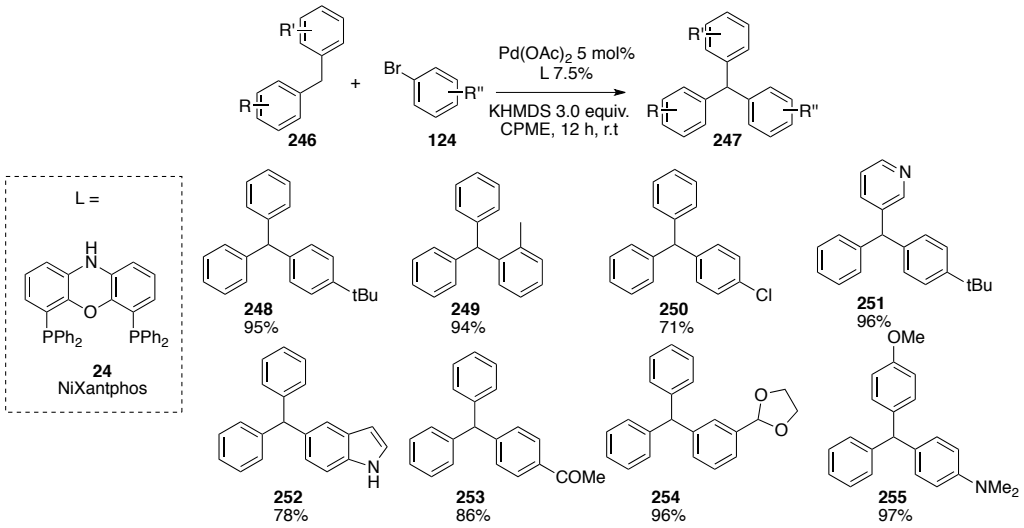
Scheme 32. Diarylation of methylheterocycles according to Li (selected examples, total scope 26 examples).[71]

To overcome the limitations encountered by the aforementioned groups, namely substrate specificity and lack of mono-arylation selectivity, Walsh reported the coupling of a series of $Cr(CO)_3$-coordinated toluene and diarylmethane derivatives in with aryl bromides (see **Scheme 33**), using $[Pd(PPh_3)_2Cl_2]$ as catalyst.[72] Chromium tricarbonyl is commonly used as a protecting group to de-activate electrophilic substitution on aromatic rings.[73]



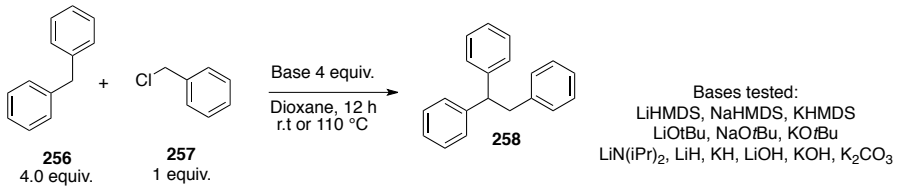
Scheme 33. Arylation of chromium tricarbonyl-activated diarylmethanes (selected examples, total scope 18 entries).[72]

Walsh subsequently focused on the chromium-free version of the benzylic arylation of diarylmethanes, trying to expand the previous report by Yorimitsu and Oshima (summarised in **Scheme 27**). High yields of the desired triarylmethanes were obtained when NiXantphos **26** was used as ligand (see **Scheme 34**).[74]



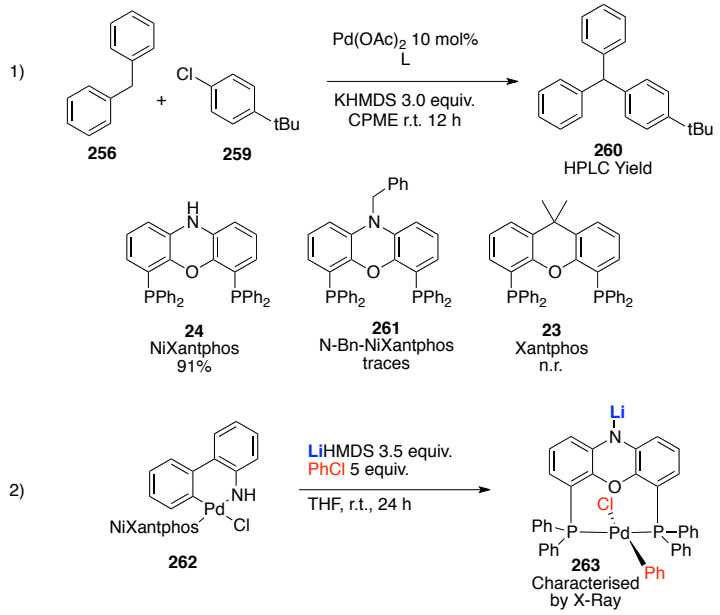
Scheme 34. Direct arylation of diarylmethanes according to Walsh (selected examples, total scope 34 entries).[74]

The authors achieved high efficiency of the protocols showed in **Scheme 34** by careful study of the deprotonation of diphenylmethane: variety of base-solvent systems were tested, trapping the anion with benzyl chloride (see **Scheme 35**). A thorough study using HTS techniques, covering many different reaction conditions, led to the conclusion that this reaction is extremely base dependent, being KHMDS the one only base capable of efficiently promoting the deprotonation both at room temperature and at high temperature; CPME was found to be the optimal solvent. Subsequent studies demonstrated that other bases, such as LiHMDS and NaHMDS, also gave satisfying results when used in combination with crown ether or chelating amines additives;[75] the effect of chelating additives has been explained by the change of nucleophilicity imposed on the main-group metal-anion species.



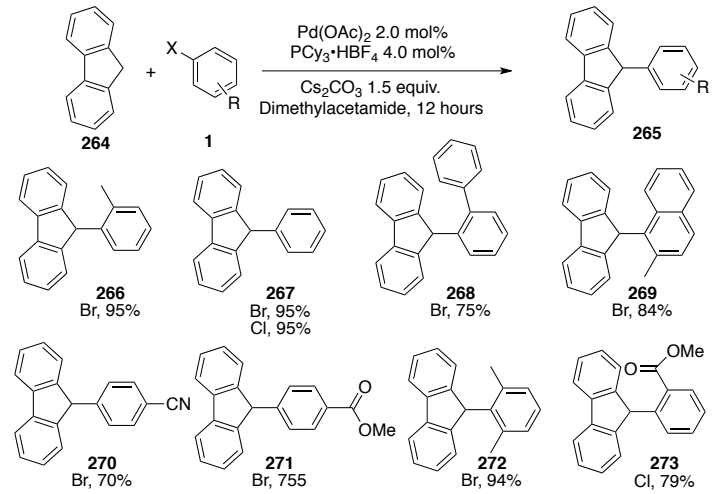
Scheme 35. Study of the deprotonation of diphenylmethane **256** performed by Walsh.[74]

The protocols reported by Walsh rely on the use of the NiXantphos ligand **270**.[76] Complexes containing this chelating diphosphine show high reactivity towards oxidative addition compared to other diphosphines displaying similar bite angle (see **Scheme 36**, equation 1). This behaviour is rationalised with the deprotonation of the free N–H bond under catalysis conditions, enhancing the electronic properties of the coordinating phosphorus atoms and therefore making NiXantphos-containing catalysts suitable for cross coupling on chloroarenes, a feature shared by few bidentate ligands (**Scheme 36**, equation 2).[77]



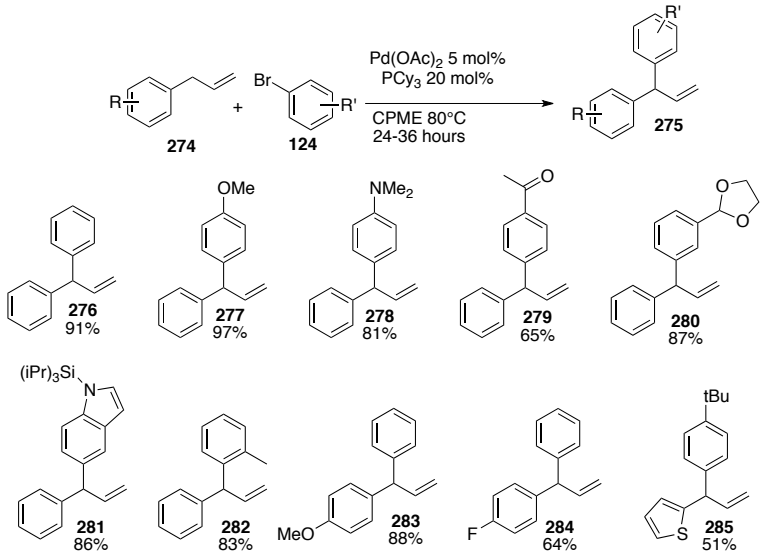
Scheme 36. 1) Comparison between Xantphos-type ligands in the coupling diphenylmethane with a chloroarene; 2) study on the coordination chemistry of NiXantphos.[77]

Wu reported on the Pd catalysed arylation of methylene-bridged polyarenes, in particular arylfluorenes: the use of Cs_2CO_3 in combination with PCy_3 allowed the preparation of a range of 9-arylfluorenes.[78] Such an approach proved valuable to the synthesis of extended π–bowls compounds as well as other polyconjugated organic materials (see **Scheme 37**).



Scheme 37. Arylation of fluorene derivatives according to Wu (Selected examples, total scope 22 entries).[78]

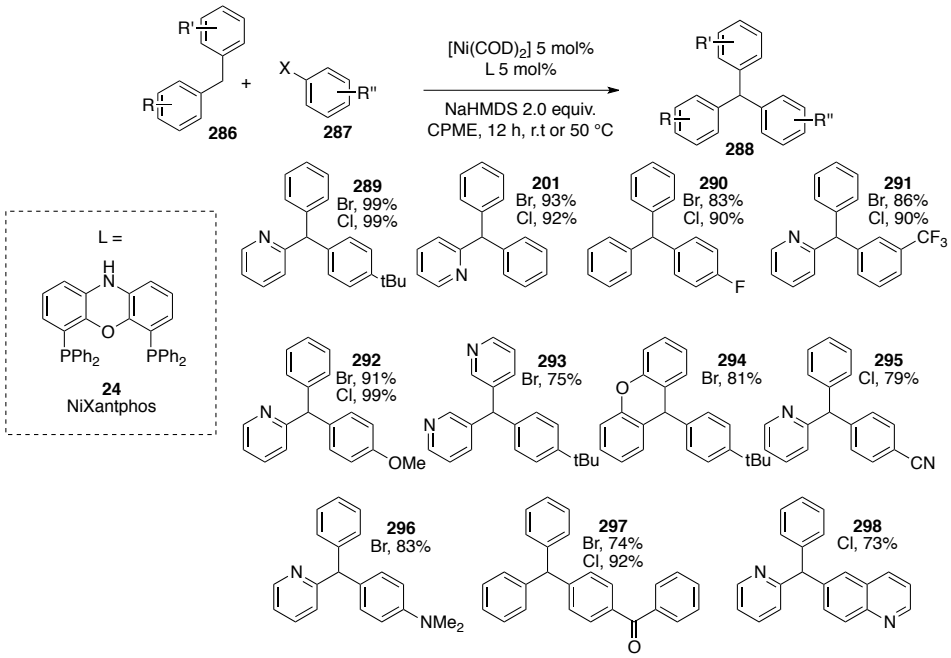
The Walsh group subsequently reported on the functionalisation of allylarenes.[79] The C–H bond is in this case activated both by the aryl ring and the vinyl moiety. The effect of the base in the deprotonation of these substrates was studied, in order to favour the deprotonative pathway over the Heck-type pathway that can take place under Pd catalysis in the presence of olefins. Different ligands afforded different selectivities between α-and γ-arylation: PCy_3 was chosen as optimal ligand, as it provided high selectivity towards arylation in α position (see **Scheme 38**).



Scheme 38. Arylation of allylarenes according to Walsh (selected examples, total scope 25 entries).[79]

In 2016, DCC processes involving benzylic C–H bonds have been reported also under Ni catalysis. Walsh demonstrated the utility of the NiXantphos ligand for the deprotonative coupling of diarylmethanes, using $[Ni(COD)_2]$ as a catalyst (see **Scheme 39**). [80] Comparison between the behaviour of NiXantphos and other Xantphos

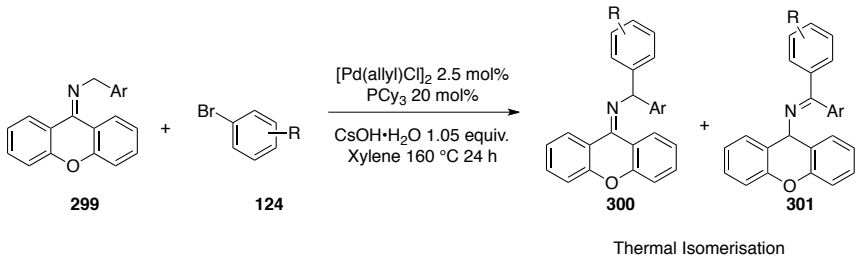
derivatives showed that both the sterics and the electronics of the P atoms are relevant, as the more electron rich and bulkier *t*Bu-Xantphos proved less effective than both Xantphos and NiXantphos, implying that steric hindrance might hamper the transmetalation step and therefore suppress the catalytic activity.



Scheme 39. Ni-catalysed arylation of diarylmethanes according to Walsh (selected examples, total scope 20 entries).[80]

1.3.2 C–H arylation of benzylamine derivatives.

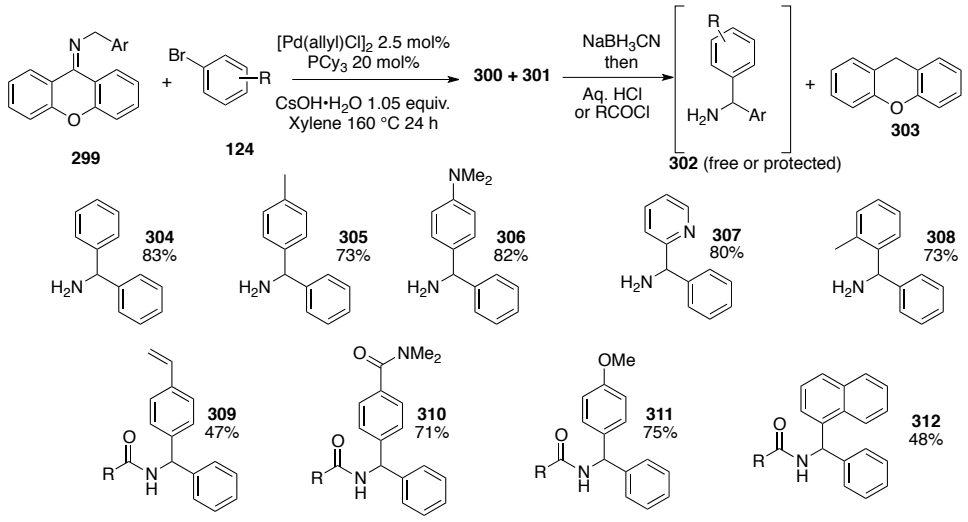
The first strategy for the C–H arylation at the benzylic position of benzylamine derivatives was reported in 2008 by Yorimitsu and Oshima. A series of Xanthone-derived benzylimines (**299**) were synthesised and treated with $[Pd(allyl)Cl]_2/PCy_3$ in the presence of $CsOH \bullet H_2O$ and chloroarenes, leading to arylation at the benzylic position (see **Scheme 40**).



Scheme 40. Isomerisation of the coupled product **309** to **310**, as observed by Yorimitsu and Oshima.

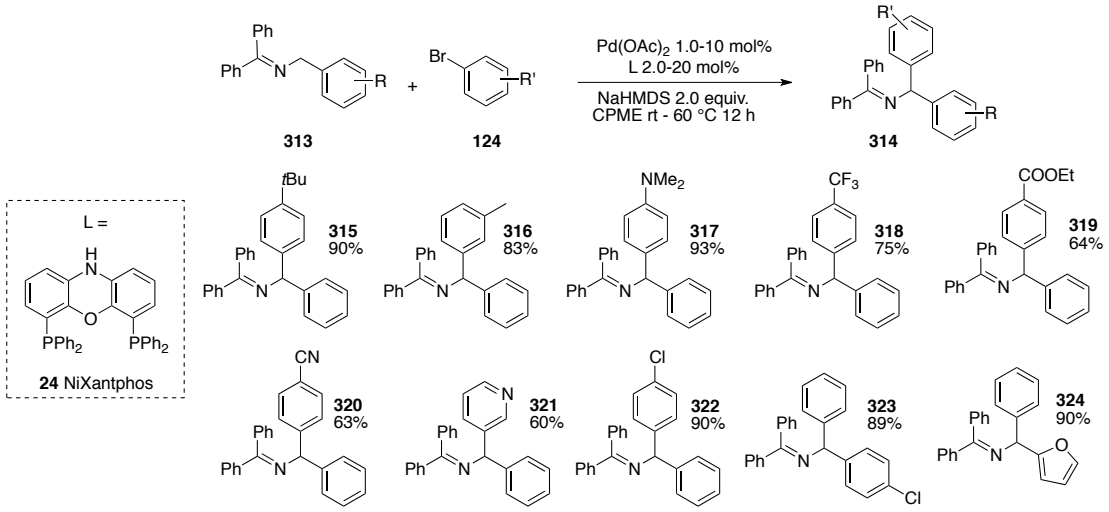
The synthetic utility of this methodology is hampered by the thermal isomerisation of the product, leading to a mixture between the desired product **309** and the

Xanthenamine-derived imine **310**. The problem of isomerisation was solved using a reduction/hydrolisis approach, with the disadvantage of an overall more complicated protocol, but higher yields and simpler purification of the desired product were achieved. [81] **Scheme 41** shows the products obtained using this strategy. A fair functional group tolerance was observed.



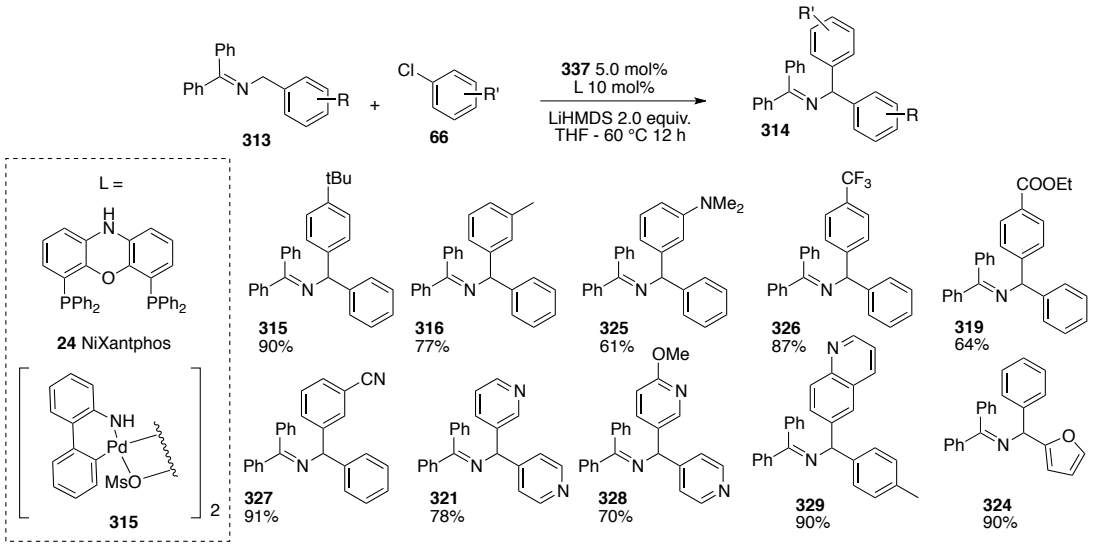
Scheme 41. One pot, three steps Pd-catalysed C–H arylation, reduction and hydrolysis to products **311** according to Yorimitsu and Oshima (complete scope).[81]

In 2014, [82] Walsh reported the deprotonative arylation of benzophenone-derived benzylimines, adopting the strategy developed for the synthesis of triarylmethane: after finding the best deprotonation conditions through HTS of base/solvent systems, they found that $Pd(OAc)_2$/NiXantphos was the best catalyst for this reaction using bromoarenes as electrophiles (see **Scheme 42**). The benzophenone-derived imines **313** used as starting materials for this protocol have the advantage of being cheaper and more readily available than the Xanthone-derived imines used by Yorimitsu and Oshima (see **Scheme 41**).



Scheme 42. Arylation of benzophenone-derived benzylmines using bromoarenes as electrophile according to Walsh (selected examples, total scope 26 entries). Slow addition of the base (as a solution 0.2 ml/h) was necessary.[82]

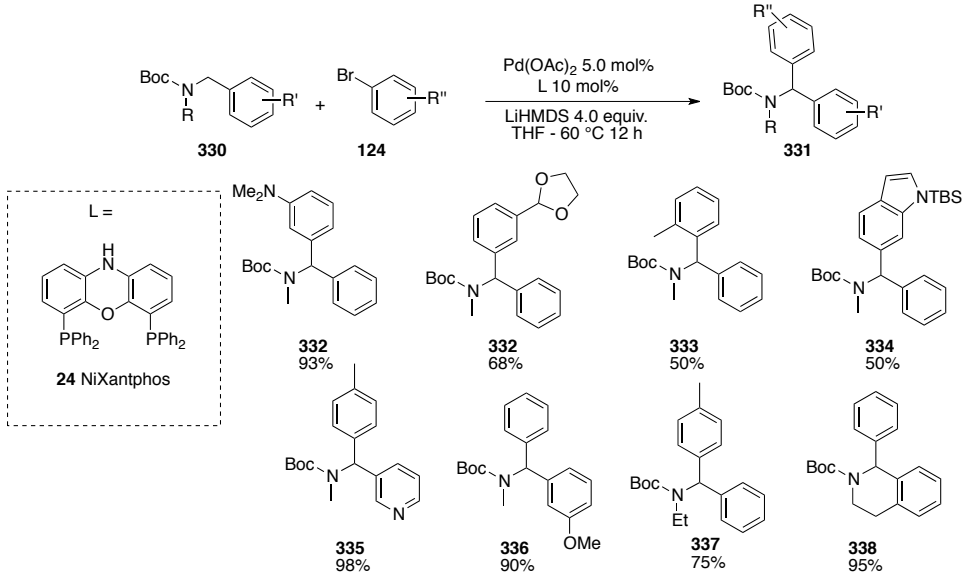
A similar catalytic system was subsequently found by Walsh to be active also for chloroarenes, only at slightly higher temperature (see **Scheme 43**).[83] The lower temperature employed for Walsh's protocols suppresses the isomerisation of the desired product observed by Yorimitsu and Oshima (**Scheme 41**), resulting in much higher yields. The disadvantage, however, lie in the need for slow addition of the base to the reaction mixture, making the whole method less user-friendly.



Scheme 43. Arylation of benzophenone-derived benzylimines using chloroarenes as electrophile according to Walsh (selected examples, total scope 29 entries). Slow addition of the base solution(0.2 ml/h) was necessary.[83]

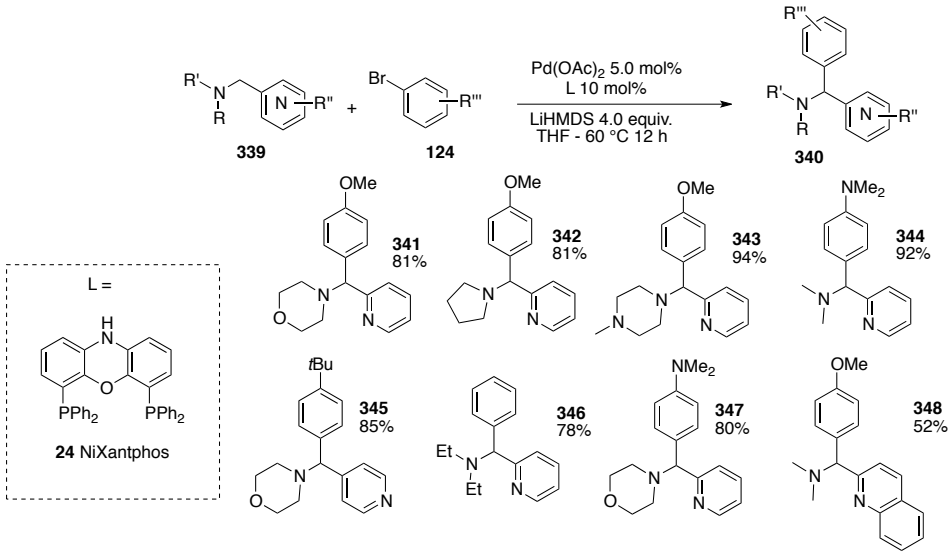
The use of imines was overcome by Walsh in 2015, when his group reported the use of a NiXantphos-based Pd catalyst for the arylation of Boc (Boc: *t*Bu-carbamate) protected

amines.[84] The protocol was applied only to methyl- and ethylamine derivatives, with the exception of the tetrahydroisoquinoline derivatives **345**, a precursor of Solifenacin (see **Scheme 44**).



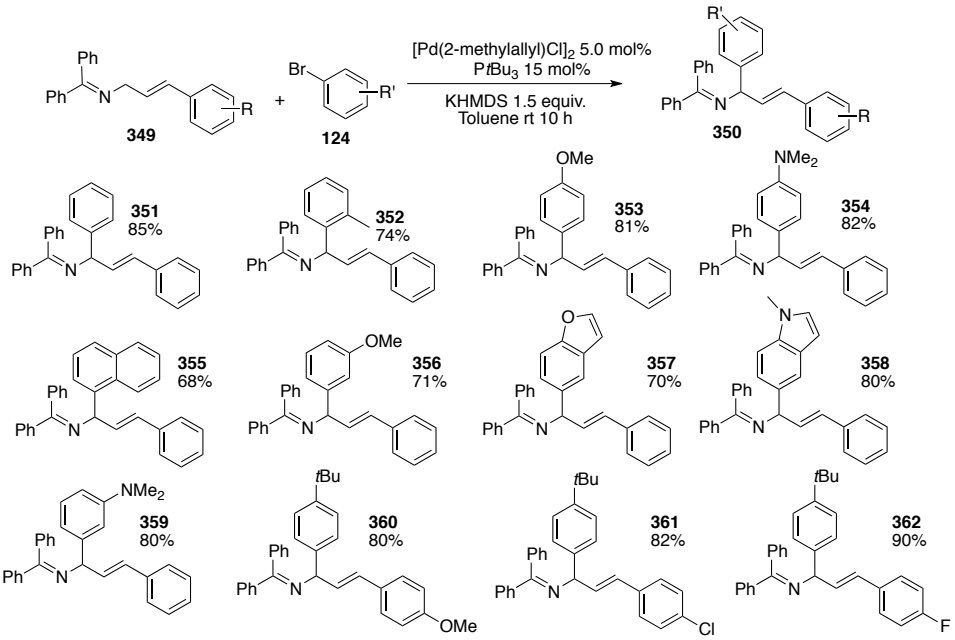
Scheme 44. Arylation of Boc-protected benzylamines according to Walsh (selected examples, [a] 7 equiv base, 30 hours, 85 °C.[84]

Walsh subsequently reported on the use of tertiary (azaarylmethyl)amines for the synthesis of (diarylmethyl)amine derivatives.[85] This method was suitable only for heterocyclic derivatives, as the presence of a pyridine or quinoline moiety was necessary to observe reactivity (see **Scheme 45**).



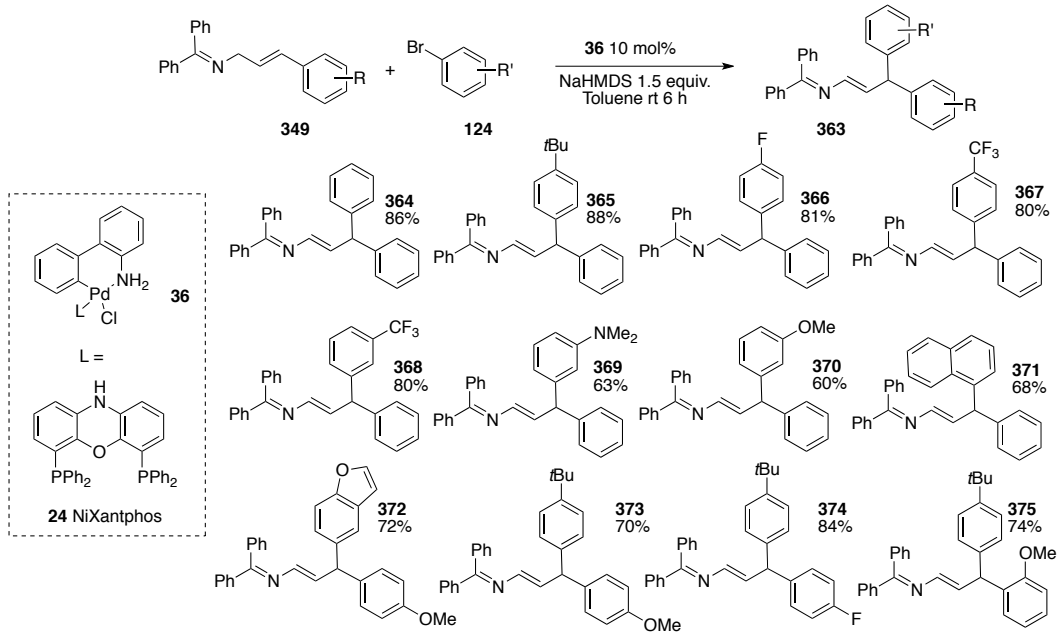
Scheme 45. Arylation of (azaryl)methylamines according to Walsh (selected examples, total scope 29 entries).[85]

Walsh reported on the deprotonative arylation of β, γ -unsaturated imines in 2016.[86] Regioselective α- or γ-arylation was achieved by tuning the reaction conditions: when using KHMDS as base, [Pd(2-methylallyl)Cl]$_2$ as metal source, and P*t*Bu$_3$ as ligand, high selectivity for α-arylation was observed (see **Scheme 46**).



Scheme 46. Arylation of enimines at the α position according to Walsh (selected examples, total scope 18 entries).[86]

The use of a pre-catalyst based on the architecture **40**, bearing NiXantphos as ancillary ligand, together with NaHMDS, led to high γ-selectivity (see **Scheme 47**).



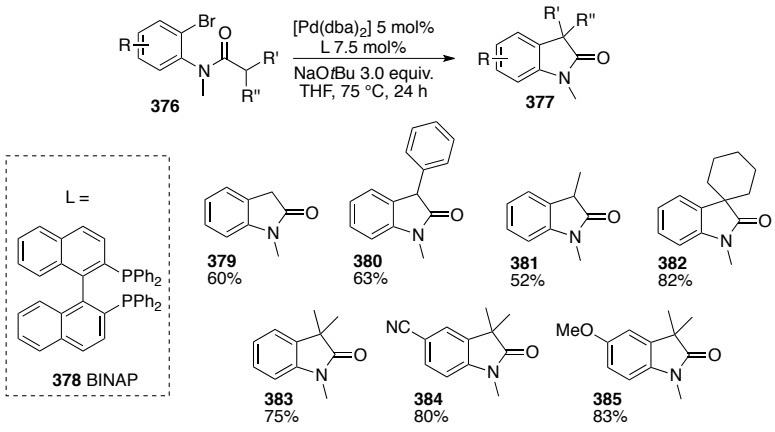
Scheme 47. Arylation of enimines at the γ position according to Walsh (selected examples, total scope 15 entries).[86]

1.4 Applications to the synthesis of heterocycles

Due to the well known chemistry of carbonyl compounds, α-arylation-type CCs have been involved in many synthetic protocols towards natural products[87] and heterocyclic scaffolds.[88] This section will focus on application of α-arylation of carbonyl derivatives for the synthesis of O- and N-containing heterocycles, mainly oxindoles, benzofurans, indoles and isoquinolines.

1.4.1 Synthesis of oxindoles

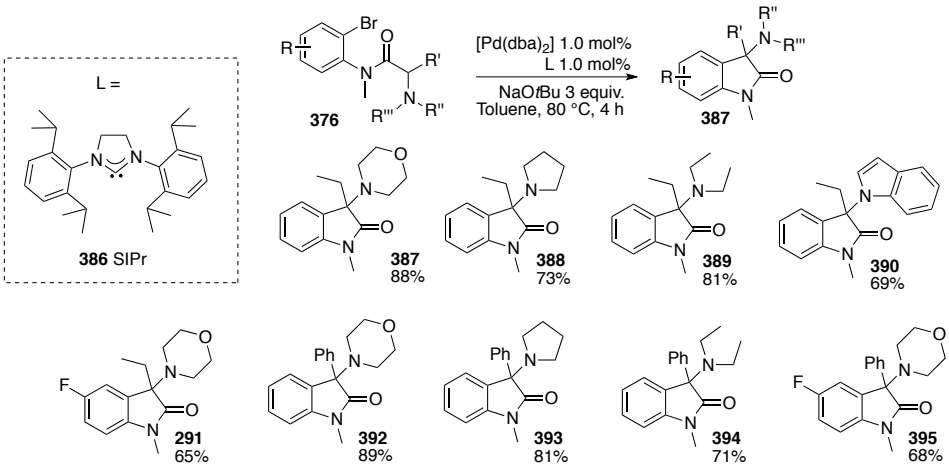
α-arylation protocols have been first applied to the synthesis of oxindole scaffolds. The employed strategy is straightforward, as it involves the intramolecular arylation of 2-haloaniline derived amides, leading to the direct formation of the desired C–C bond. This strategy had been explored by Hartwig in the synthesis of a small range of substituted oxindoles (see **Scheme 48**). The authors used a first generation catalyst (a Pd source + a bidentate ligand, BINAP) for the intramolecular coupling of 2-bromoaniline derived amides **376**.[89] Noticeably, the synthesis of tetrasubstituted carbons at the 3 position afforded higher yields compared to the corresponding tertiary carbons, probably due to the side reactions arising from the subsequent deprotonation at that position, still enolizable when trisubstituted. This feature triggered the research about enantioselective synthesis of tetrasubstituted oxindoles with good success, achieveing high yields and enantiopurity over a broad range of target compounds.[90]



Scheme 48. Synthesis of oxindoles according to Hartwig (complete scope).[89]

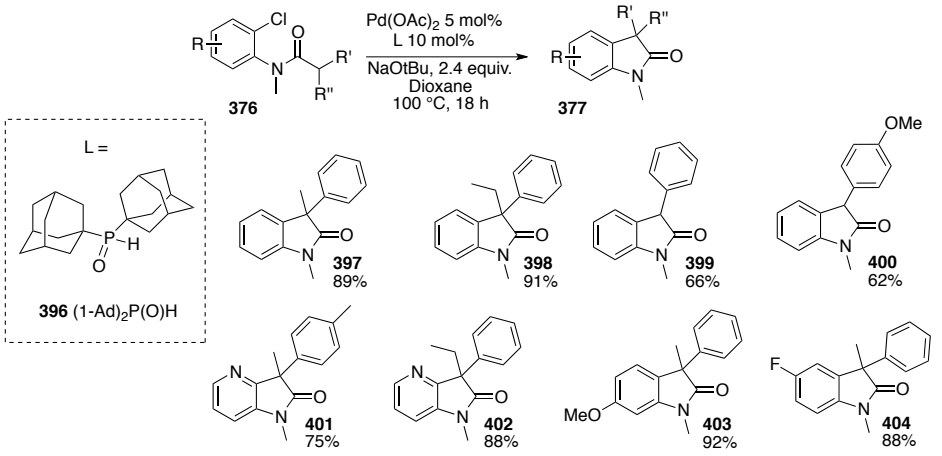
Marsden subsequently reported on a much more efficient method to perform this reaction.[91] Using an NHC ligand, they were able to synthesise similar compounds

using catalyst loadings as low as 0.1 mol%. A scope of medicinally interesting 3-aminooxindole has been prepared in this way (see **Scheme 49**).



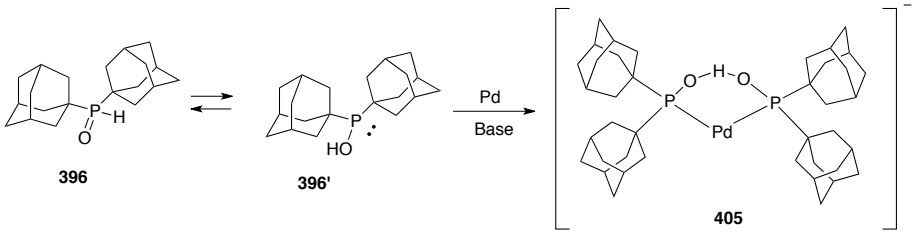
Scheme 49. Synthesis of oxindoles according to Marsden (complete scope).[91]

In 2009, Ackermann reported on the use of 2-chloroaniline-derived amides for this intramolecular coupling (see **Scheme 50**). The scope reported was much wider, and included some examples of 4-aza-oxindole derivatives (**401-402**). Also in this case, the use of α-disubstituted amides resulted in better yields.[92]



Scheme 50. Synthesis of oxindoles according to Ackermann (selected examples, total scope 18 entries).[92]

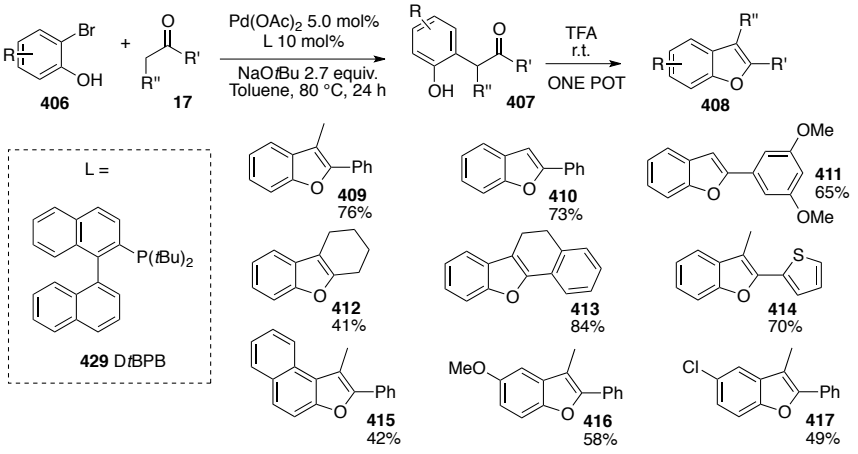
The use of the phosphine oxide ligand **396** was known in a range of challenging cross couplings: its mode of action was proved by Ackermann to involve the *in situ* formation of a chelating, bidentate adduct derived from the tautomerisation of the PO double bond and its subsequent deprotonation, resulting in the bis-ligated, Pd complex **405** (see **Scheme 51**).[93]



Scheme 48. Formation of the active Pd species using phosphine oxide **396** as ligand.[93]

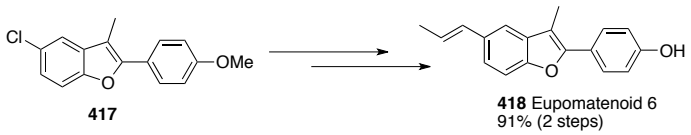
1.4.2 Synthesis of benzofurans

Protocols for the synthesis of benzofurans have been initially reported by Miura[94] and the group of San Martin and Dominguez.[95] This strategy is based on a two step, bis-deprotonative C– and O–arylation of ketones. Although their significant novelty in the context of heterocycles synthesis, these protocols suffer many drawbacks, most importantly high reaction temperature (160 °C) and limited regioselectivity. A similar strategy was reported by Willis.[96] A more convenient method for the preparation of benzofurans was reported by Eidamshaus and Burch in 2008, who developed a one pot α-arylation / condensation reaction of ketones and 2-bromophenols (see **Scheme 52**) using the D*t*BPB ligand, an example of bulky, electron rich diarylphosphine.[97]



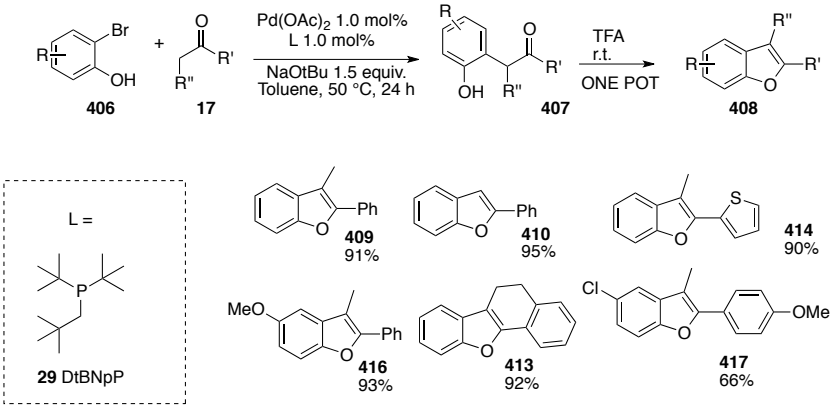
Scheme 52. Synthesis of benzofurans according to Burch (selected examples, total scope 20 entries).[97]

In the same report, the authors also showed the role of their reaction in the synthesis of the bioactive product Eupomatenoid 6, using their one pot protocol as the key step (see **Scheme53**). This adds value to a synthetic strategy that already shows a good functional group tolerance.



Scheme 53. Synthesis of Eupomatenoid 6 using the arylative protocol developed by Burch.[97]

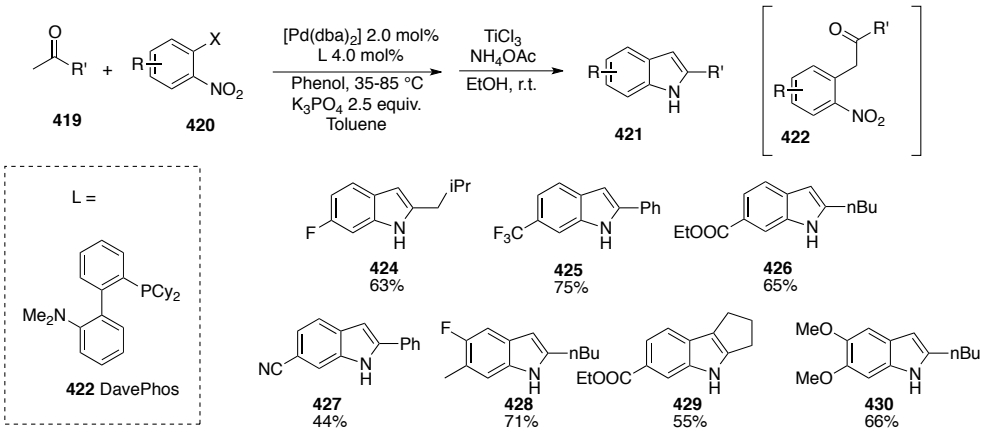
Shaughnessy successfully applied the catalytic system he reported in 2014 to this transformation (see **Scheme 54**).[50] The use of a simpler trialkylphosphine (D*t*B*n*PP, **419**), as well as lower reaction temperatures (50 °C vs. 80 °C), lower catalyst loadings (1 mol% vs 5 mol%) and generally improved yields make this protocol extremely valuable. Moreover, the intermediate **417**, used in the synthesis of Eupomatenoid 6, was obtained in better yield (compared to that reported by Burch) using this protocol.



Scheme 54. Synthesis of benzofurans according to Shaughnessy (Selected examples, total scope 12 entries).[50]

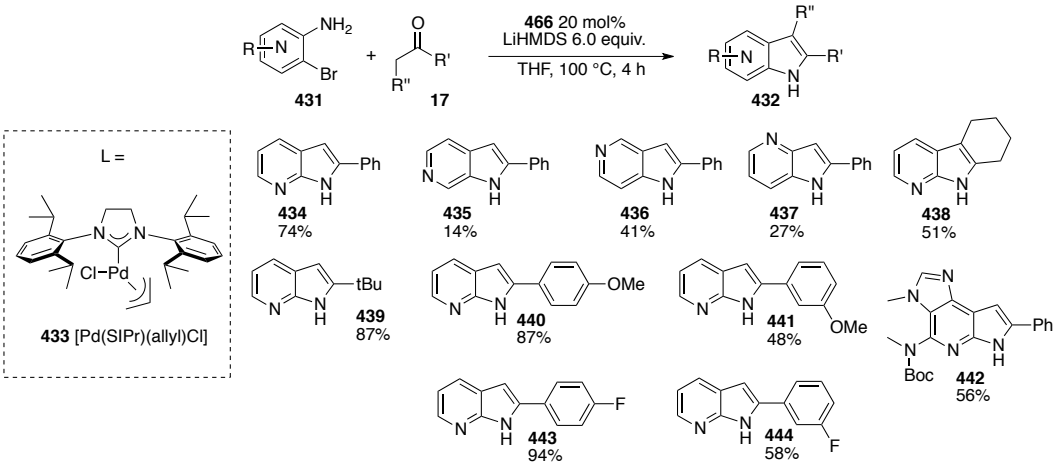
1.4.3 Synthesis of indoles and carbazoles

The first example of α-arylation of carbonyls in the synthesis of indoles was reported by Buchwald in 2002.[98] The monoarylation of acetophenone derivatives with 2-chloronitroarenes leads to the intermediate **422**, which upon reduction with $TiCl_3$ and condensation of the newly formed amine with the carbonyl of the ketone gave a wide range of 2-substituted, N-unprotected indoles. The use of 0.3 equivalents of phenol additive provided improved yields in the ketone arylation step (see **Scheme 55**). The authors postulate an interaction between the ketone, the phosphate base and the phenol in the deprotonation step, making the protocol suitable for substrates bearing a nitro group as substituent.



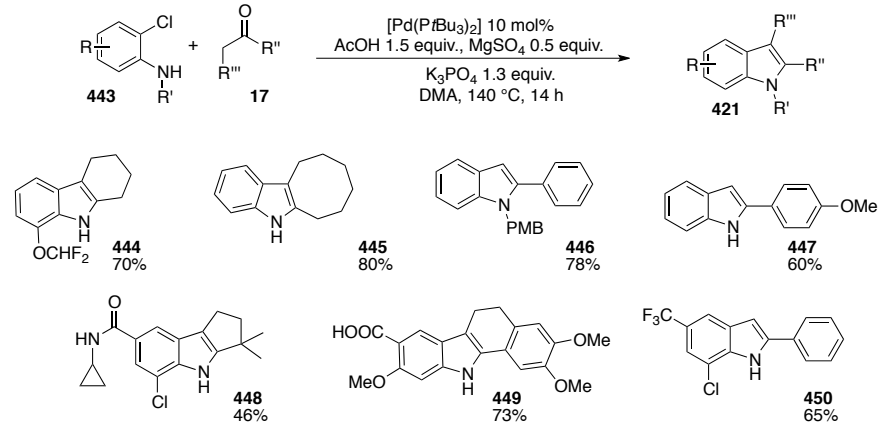
Scheme 55. Two-step ketone arylation-reductive cyclisation for the synthesis of indoles according to Buchwald (selected examples, total scope 21 entries).[98]

The direct synthesis of N-unprotected 2-substituted azaindole derivatives from 2-bromoaniline and a ketone *via* enolate arylation was studied by Spergel.[99] This strategy is extremely appealing, because of the great availability of a wide range of starting materials, both ketones and 2-bromoaniline derivatives, and for its feature of producing N-unprotected compounds directly from the palladium-catalysed reaction. On the other hand, the presence of a free -NH_2 moiety on the electrophilic coupling partner creates problems with the selectivity between N– and C–arylation, therefore limiting the efficiency and the scope of this approach. **Scheme 56** summarises such features: the authors were able to synthesise complex compounds such as the polyclic derivative **442**, but the catalyst loading was high (20 mol% of the relatively expensive, NHC-containing complex **433**). Moreover, when the NH_2 moiety was not electronically unactivated, very low yields were observed (entries **435** and **437**).



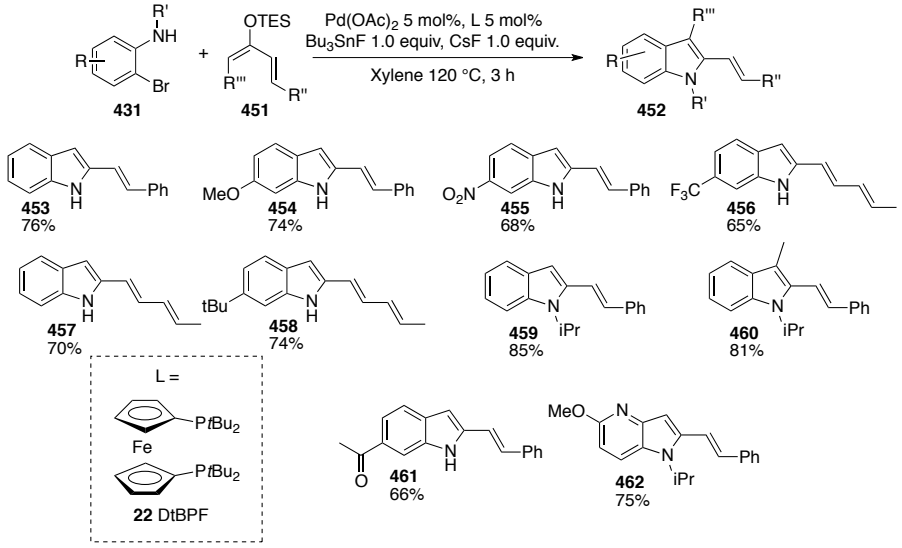
Scheme 56. Synthesis of azaindoles according to Spergel (selected examples, total scope 16 entries).[99]

A similar intermolecular approach was previously reported by Nazarè, whose group employed [Pd(PtBu$_3$)$_2$] as catalyst and a mixture of K$_3$PO$_4$ and acetic acid as additives, in the presence of a drying agent. Despite the high catalyst loading required (10 mol%) and the high temperature, this method shows a great functional group tolerance and impressive flexibility, allowing the preparation of highly functionalised compounds (see **Scheme 57**). The additional advantage of not requiring any pre-functionalisation of the substrates makes it relatively practical.[100]



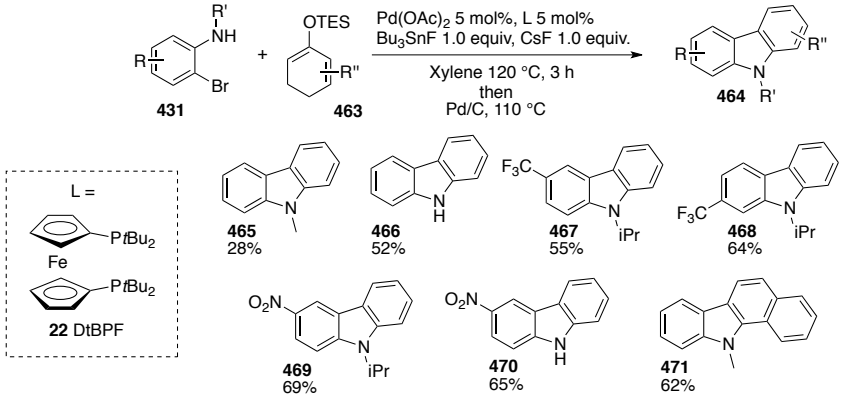
Scheme 57. Synthesis of indoles according to Nazarè (selected examples, total scope 21 entries).[100]

In 2015, Kapur reported a related arylation of enone enolates.[101] In order to avoid N-arylation and to increase the functional group tolerance, the enolate was not produced by deprotonation, but by deprotection of a silylenol ether with Bu$_3$SnF and CsF and subsequent arylation of the tin enolate. The protocol proved useful in the synthesis of various 2-vinyl substituted indole derivatives (see **Scheme 58**).



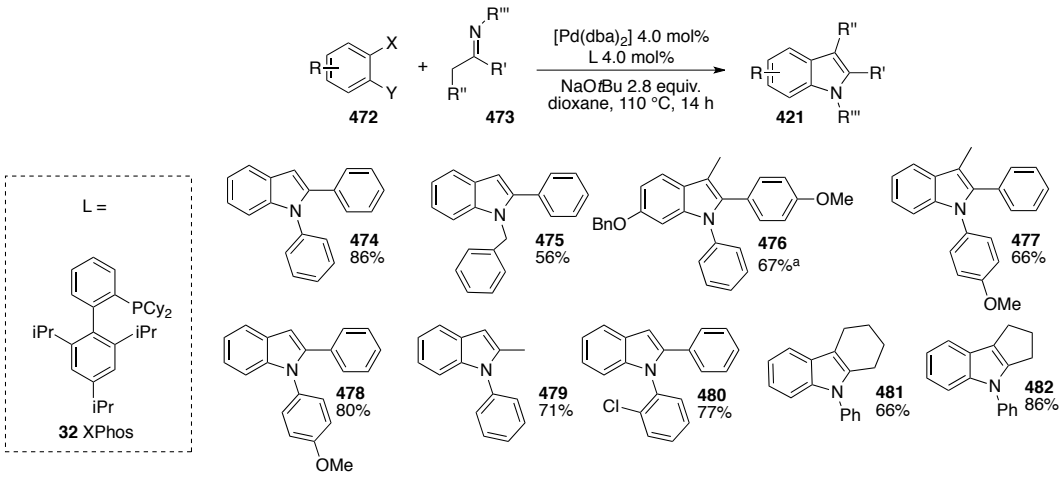
Scheme 58. Synthesis of 2-vinylindoles according to Kapur (selected examples, total scope 23 entries).[101]

When cyclohexenone-derived silylenolethers were used as starting material, it was possible to obtain carbazole derivatives by simple dehydrogenation of the product, under Pd/C catalysis (see **Scheme 59**).



Scheme 59. One pot synthesis of carbazole derivatives according to Kapur (selected examples, total scope 16 entries).[101]

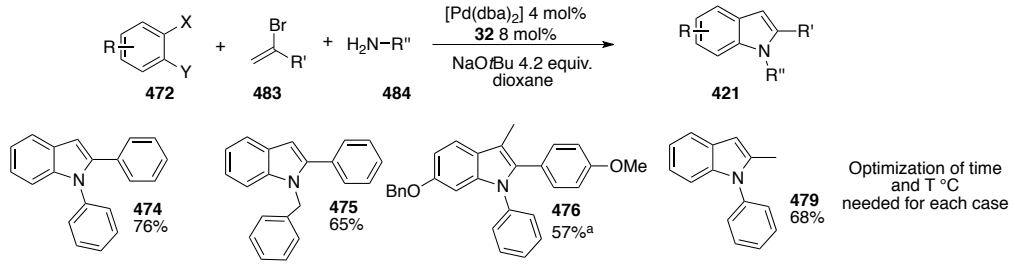
In 2007, Barluenga reported the synthesis of indole derivatives through sequential α- and N-arylation of ketoimines with *o*-dihaloarenes (see **Scheme 60**).[102] The reaction works with *o*-dibromo- and *o*-dichloroarenes (entry **476**), as well as with more substituted 2-chlorobromoarenes. Variously 1,2,3-substituted indoles were obtained in this way. Acetone-derived imines were also tolerated (entry **479**).



Scheme 60. Synthesis of indoles according to Barluenga (selected examples, total scope 14 entries). X = Y = Br unless otherwise stated; [a] 2-chloro-4-benzoxy-bromobenzene was used as electrophile.[102]

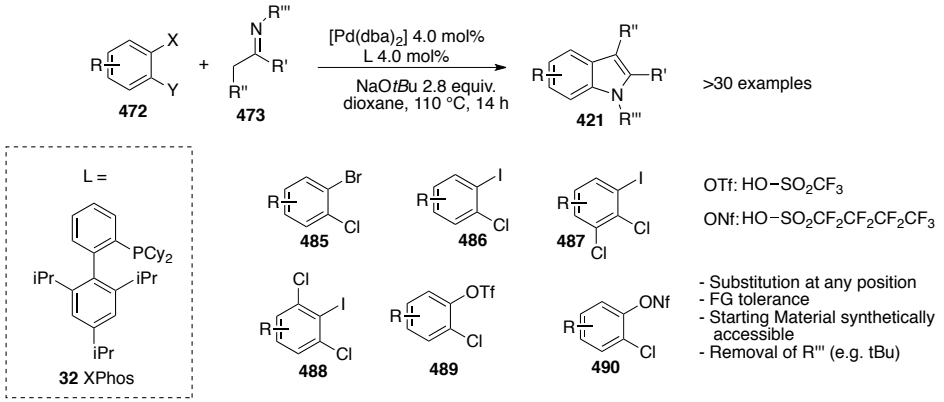
In the same report, a 3-component reaction using an amine, a bromoalkene and a dihaloarene was also reported. Although such reactivity would be advantageous, because it avoids the need for the synthesis of the imine in a separate step, the need for

optimisation in almost each single case, and the lower yields, limited the utility of this approach (see **Scheme 61**)



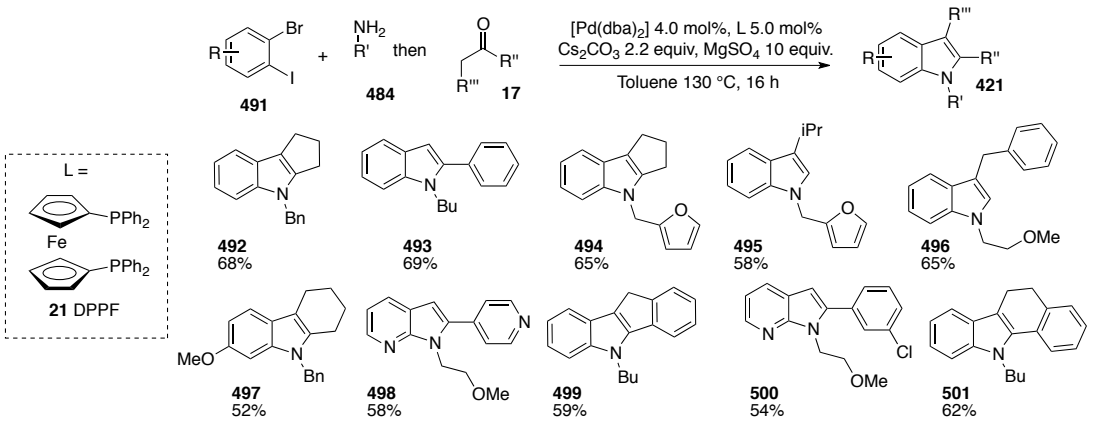
Scheme 61. Three component synthesis of indoles according to Barlunega.[102]

A subsequent report by the same authors expanded the scope of the α-arylation of the imine to a very wide range of coupling partners:[103] N-*t*Bu imine gave easy-to-deprotect indole derivatives; 1,2,3-trihaloarenes were suitable substrates, allowing the synthesis of both 4- and 7-halosubstituted compounds; the use of 2-chlorophenol derivatives, such as 2-chlorotriflates and 2-chlorononaflates, was also possible (see **Scheme 62**). In particular the use of the nonaflate group as electrophilic coupling partner resulted in a wide applicability of this method.



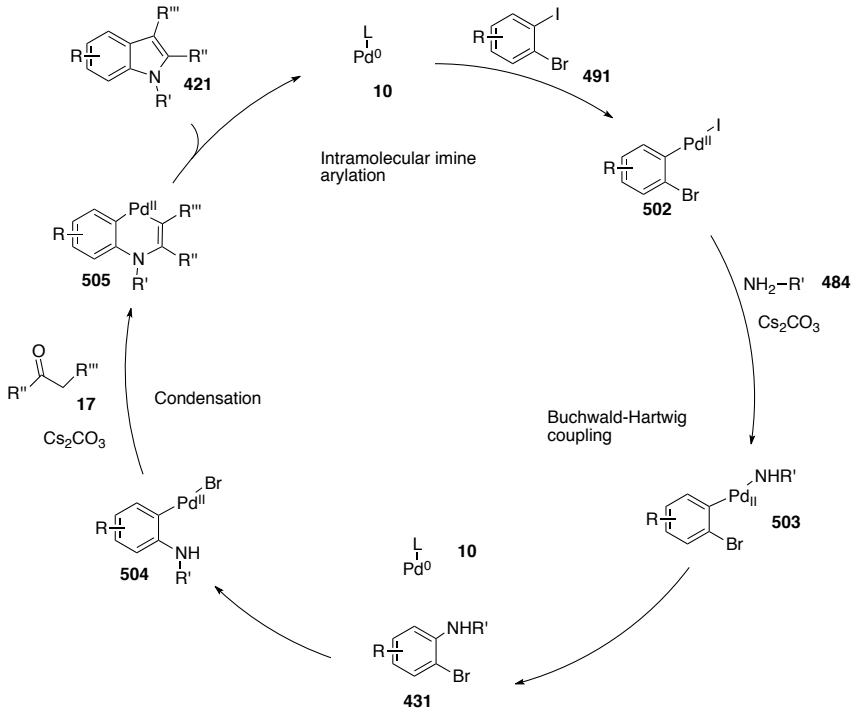
Scheme 62. Expanded scope of electrophiles used for the synthesis of indoles according to Barluenga.[103]

Kurth reported an expanded version of this strategy involving *o*-dihaloarenes, primary amines and carbonyl compounds in a three-components synthesis of indoles and azaindoles (see **Scheme 63**).[104] Interestingly, this method allows the coupling of aldehyde-derived enolates, whose use is more challenging because of their inherently higher reactivity, often leading to undesired side reactions. Heterocyclic moieties were tolerated on all the components of the reaction. On the other hand, the isolated yields of the reaction ranged between 50% and 70%.



Scheme 63. Synthesis of indoles according to Kurth (selected examples, total scope 14 entries).[104]

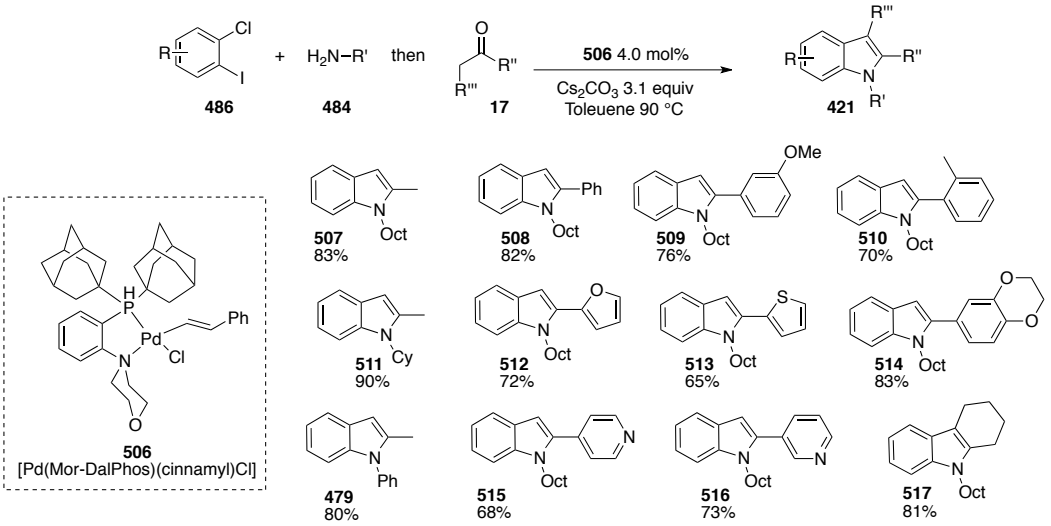
Remarkably, the order of events was determined by the authors, who performed a number of control experiments. Their conclusion was that a Buchwald-Hartwig amination, affording intermediate **546**, is the first step of the catalytic cycle, followed by condensation of the resulting secondary amine with the ketone and subsequent deprotonation affords the palladacycle **548**, which upon reductive elimination gives the desired product and the Pd^0 catalytic species (see **Scheme 64**).



Scheme 64. Mechanism of the synthesis of indole according to Kurth: sequential Buchwald-Hartwig / condensation /ketone arylation.[104]

The three-component reaction, pioneered by Barluenga and Kurth, between amine, dihaloarene and ketone was studied by Stradiotto in 2015 (**Scheme 65**).[105] At similar palladium loadings, their catalytic system provided higher yields at lower

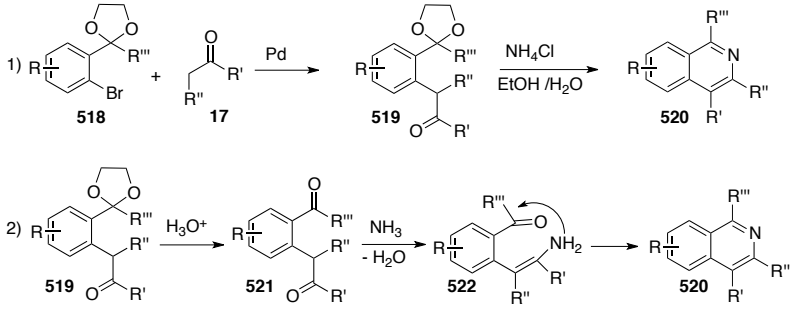
temperature, using the more challenging 2-chloroiodoarene electrophiles, delivering a wide range of indole derivatives.



Scheme 65. Synthesis of indoles according to Stradiotto (Selected examples, total scope 29 entries).[105]

1.4.4 Synthesis of isoquinolines

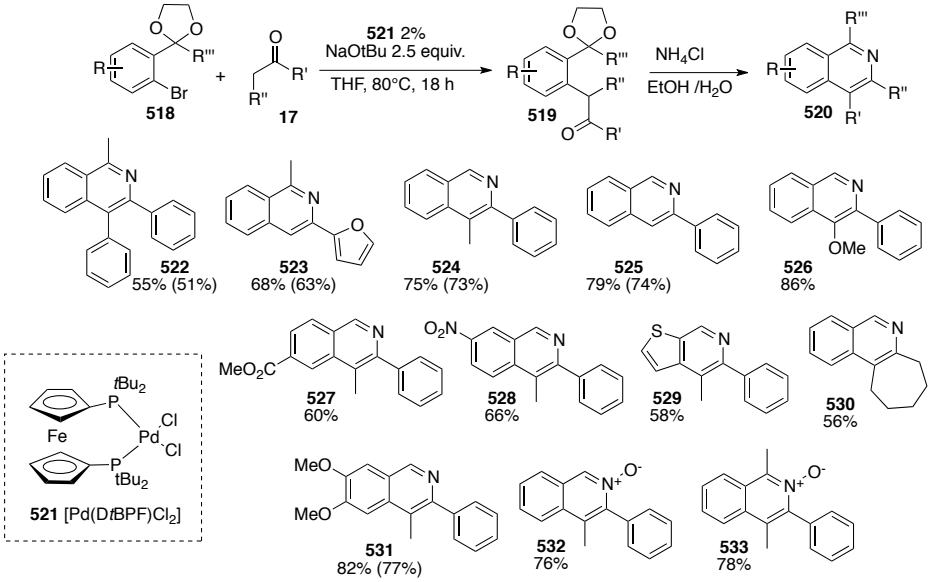
The use of the α-arylation of ketones as key step in the synthesis of isoquinolines was reported by Donohoe in 2012.[106] This original approach starts with the arylation of a ketone using a bromoarene of general formula **518** (see **Scheme 66**, equation 1). Treatment of this dicarbonyl compound with NH_4Cl generates the isoquinoline **520** *via* nucleophilic attack of ammonia on one of the carbonyl group of the intermediate **519**, followed by intramolecular attack of the enamine **522** on the other carbonyl moiety and subsequent aromatisation (**Scheme 66**, equation 2).



Scheme 66. 1) Strategy for the synthesis of isoquinolines according to Donohoe 2) Reaction mechanism.[106]

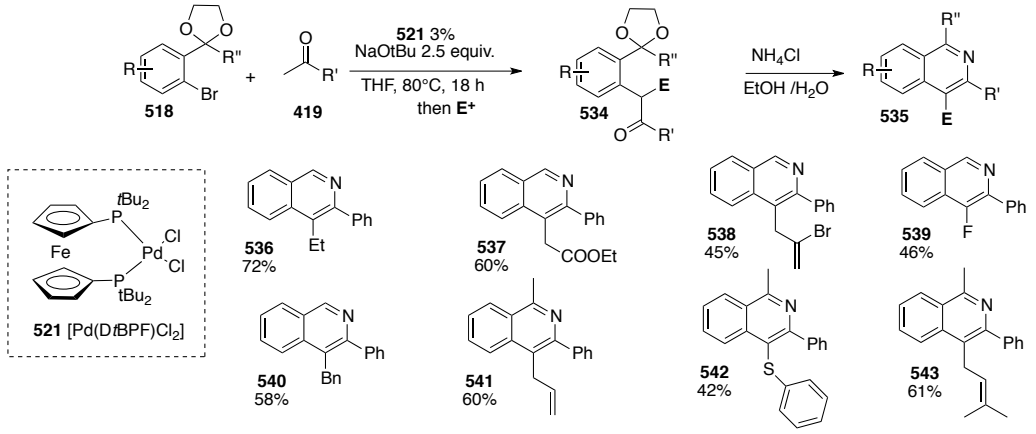
A wide scope of substituted isoquinoline derivatives were prepared by Donohoe following this protocol, which shows a good functional group tolerance (entries **527** and **528**) including the use of heterocyclic bromoarenes, such as the thienopyridine **529**; hydroxylamine was also suitable for the cyclisation step, generating isoquinoline N-

oxides **532** and **533**. This synthetic strategy was also suitable for one-pot procedures, with only slight loss in the final isolated yield (values in parenthesis in **Scheme 67**).



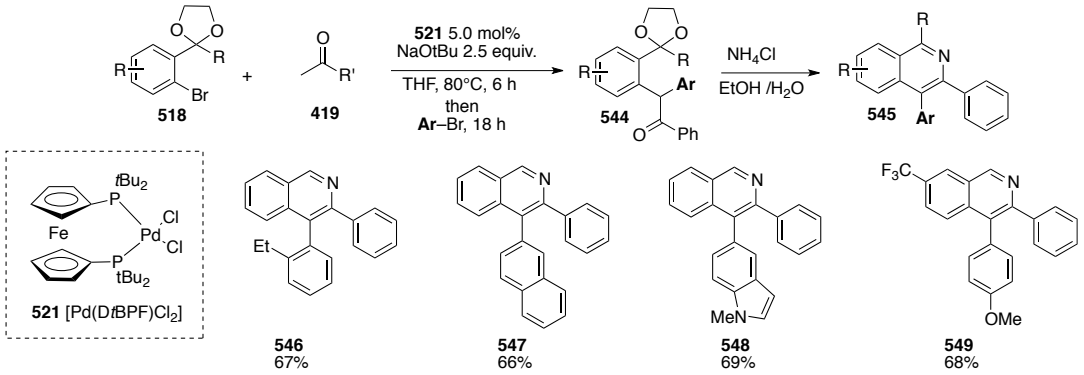
Scheme 67. Synthesis of isoquinolines according to Donohoe (selected examples, total scope 24 entries). The number in parenthesis is the isolated yield for the one-pot procedure.[106]

Donohoe subsequently extended the protocol, introducing an additional step in the reaction sequence. After the cross coupling takes place, using an acetophenone derivative **419** as pro-nucleophile, the authors further functionalised intermediate **519** by reacting it with various electrophiles. This strategy allows the introduction of functionalities such as vinyl bromides (**538**), esters (**537**) and thioethers (**542**). Such one-pot procedure enables preparation of variously 7-substituted isoquinolines starting from the same CC partners and an external electrophile (see **Scheme 64**).[107]



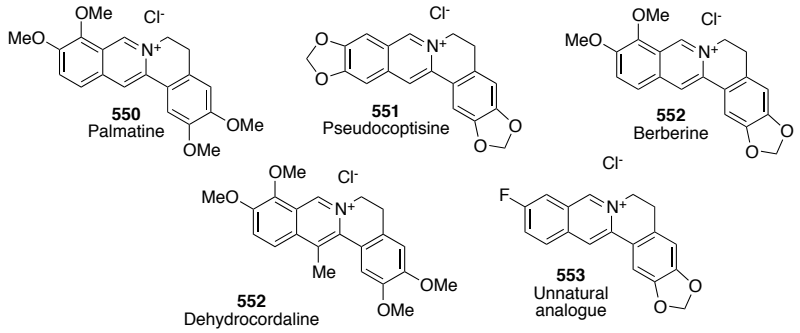
Scheme 68. Sequential ketone arylation /electrophilic substitution/cyclisation for the synthesis of 7-substitued isoquinolines according to Donohoe (selected examples, total scope 14 entries).[107]

The modular functionalization can also involve a subsequent cross coupling reaction, leading to 7-arylisoquinolines. The three steps of the reaction (two distinct arylations and the cyclisation with ammonia) could be carried out in one pot, with generally good yields (see **Scheme 69**).



Scheme 69. Sequential diarylation/cyclisation for the synthesis of 7-arylisoquinolines according to Donohoe (selected examples, total scope 9 entries).[107]

Donohoe reported the application of the above-mentioned annulative approach for the synthesis of the protoberberine class of natural products.[108] The flexibility of this approach is highlighted by the wide range of natural and non-natural analogues that it can provide, and shows that carbonyl arylation still has a significant untapped potential to discover and exploit (see **Scheme 70**).



Scheme 70. Elements of the protoberberine class of alkaloids synthesised by Donohoe.[108]

1.5 Outcome

The increasing attention received by the area of DCC methodologies enabled their development, making them one powerful tool to access biologically or industrially relevant compounds. The α-arylation of carbonyls is an appealing synthetic method, given the possibility to further derivatise the carbonyl moiety, and is already considered one important branch of cross coupling chemistry; the arylation at benzylic position, on the other hand, is far less studied, but its utility is emerging in the last few

years, and its development would give the synthetic community an easy, modular access to important pharmacophores and molecular materials.

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2 Large-yet-flexible NHC ligands in the Pd-catalysed α-arylation of ketones

2.1 The use of sterically demanding NHC ligands in Pd-catalysed CC chemistry.

The paramount importance of CC chemistry for modern organic synthesis is epitomised in the escalating progress achieved in the field of ancillary ligands.[1] The quest for increasingly efficient catalytic system has prompted the study of the structure-activity relationship of such ligands, resulting in the development of analytical and computational tools enabling the measurement of their steric and electronic properties and, to some extent, the prediction of their catalytic activity (see section **1.1.3** of this thesis).

The use of bulky phosphines for CC chemistry was pioneered by Buchwald and Hartwig during the '90s.[2] Specifically, the use of phosphine ligands in the Pd catalysed α-arylation of ketones is reported by Buchwald, Kwong, Colacot, Stradiotto and Shaughnessy (among others), as summarised in **Chapter 1** (see **Figure 1**).[3]

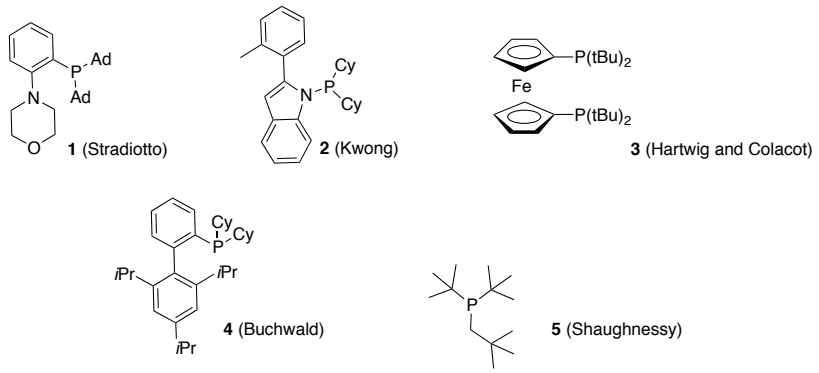


Figure 1. Selected phosphine ligands reported for Pd catalysed α-arylation of ketones.

NHC ligands are known to be efficient ancillary ligands in CC chemistry since Nolan's seminal report on their use for the Suzuki-Miyaura reaction.[4] In 2004, Glorius and coworkers introduced the concept of "flexible steric bulk" while reporting the outstanding activity of the Ibiox class of ligands in the Suzuki-Miyaura reaction.[5] Subsequently, more reports on the use of NHC-based catalysts have been published by Organ, Dorta, and Markò.[6] The main examples of the systems mentioned above are

reported in **Fig. 2**. The utility of these catalytic systems has been proved in different CC reactions, including the Buchwald-Hartwig,[7] Negishi,[8] and sulfination reaction.[9]

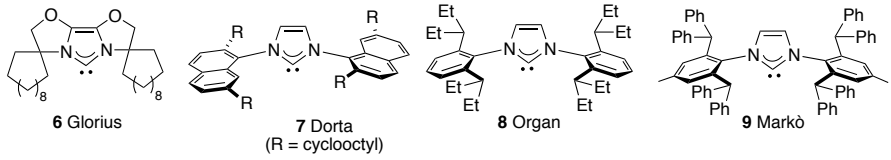


Figure 2. Bulky-yet-flexible NHC ligands used for CC chemistry.

The good activity of IPr-based catalysts in the α-arylation of ketones was first reported by Nolan in 2002, in a seminal paper describing the first [Pd(NHC)] well-defined pre-catalyst for CCs.[10] Since then, Nolan and other authors reported a variety of IPr-based pre-catalysts, such as the PEPPSI-like complexes **10** and **11**, reported respectively by Shi and Shao.[11]

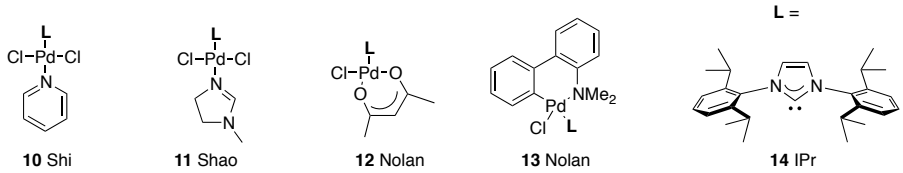


Figure 3. Examples of NHC-based Pd catalysts for α-arylation of ketones.

Curiously, at the time we began working on this project, the study of the effect of NHC ligands bulkier than IPr **14** in the α-arylation reaction was an underdeveloped field.The NHC-based Pd pre-catalysts in our hands display outstanding activity in the Suzuki-Miyaura and Buchwald-Hartwig reactions, even at low catalyst loading.[12] Obviously, the development of more efficient catalytic methods for the synthesis of α-arylketones would be highly beneficial, especially for industrial applications, as it would make the synthesis of such class of compounds cheaper and more environmentally sustainable. We therefore focused our attention on pre-catalysts developed by our group, mainly based on the IPr* ligand (complexes **18** and **22** in **Figure 4**), and on the ITent series of NHCs (complexes **15-17** and **19-21** in **Figure 4**). The main difference between the former and the latter lies in the substitution at each of the 2-positions of their N-bound aryl rings: while the IPr* species bears a bulky diphenylmethyl moiety, the ITent ligands are decorated with increasingly long alkyl chains: 3-pentyl (IPent), 4-heptyl (IHept), and 5-nonyl (INon).

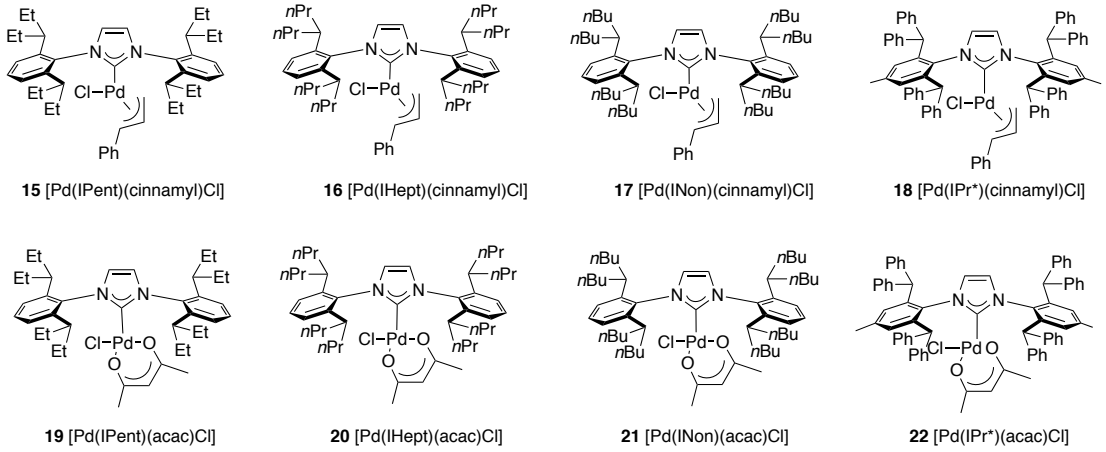


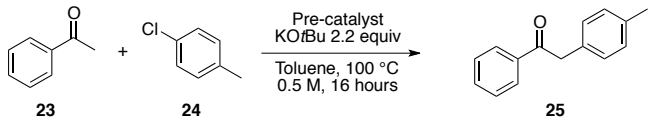
Figure 4. Pd pre-catalysts developed by the Nolan group.

Pre-catalysts based on these ancillary ligands were screened, and successfully employed in the α-arylation of aryl-alkyl-ketones.

2.2 Screening for the optimal conditions.

With an aim to determine suitability of IPr* or ITent ligands for arylation of ketones, acetophenone, acetophenone and 4-chlorotoluene were chosen as model coupling partners for the initial screening and optimisation of the reaction conditions. As discussed in **Section 1.2**, the selective arylation of methylketones as pronucleophiles is considered difficult, as the coupling product often undergoes subsequent arylation, thus lowering the selectivity due to formation of *bis*-arylated product. The choice of a challenging ketone substrate, together with the use of the sterically unhindered haloarenes was made under the assumption that once the conditions for a relatively difficult reaction have been found, they would allow the coupling of a wide range of other, less challenging substrates.

Table 1. Selection of the precatalyst.



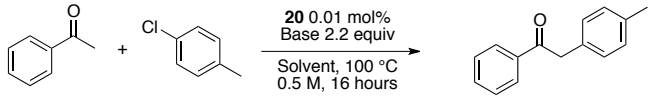
23 24 25

Entry	Pre-catalyst	Pd loading (mol %)	Conversion %[a]
1	**15**	1.0	99
2	**15**	0.1	99
3	**18**	0.1	12
4	**19**	0.1	13
6	**15**	0.02	99
7	**16**	0.02	99
8	**17**	0.02	75
9	**19**	0.02	99
10	**20**	0.02	99
11	**21**	0.02	86
12	**15**	0.01	2
14	**16**	0.01	**22**
15	**19**	0.01	3
16	**20**	0.01	22

Conditions: 23 (0.7 mmol, 1.4 equiv), 4-Chlorotoluene (0.5 mmol, 1.0 equiv), KO*t*Bu (1.1 mmol, 2.2 equiv), catalyst (0.01 mol% or 0.02 mol%), in toluene (1mL), 100°C, 16h. [a] Conversion of 4-Chlorotoluene was measured by GC.

The study of the reaction was initiated using complex **15**, [Pd(IPent)(acac)Cl], at 1 mol% catalyst loading. This coupling provided complete conversion to the desired product. Subsequent screening of ITent- and IPr* based pre-catalysts **15-22** was then performed. IPr* showed poor catalytic activity at low catalyst loading (0.1 mol%) while IPent gave high conversions of 99% (entries **3** and **4**). Comparing the whole ITent family, INon-based pre-catalysts were less active than the IPent- and IHept congeners at 200 ppm catalyst loading (entries **8** and **11**), while at 100 ppm only [Pd(IHept)(acac)Cl] **20** was catalytically active (entry **14**). This pre-catalyst was also proved to be the most active in the Buchwald-Hartwig CC.[12] It is noteworthy to mention that very few examples of catalysts active at a loading lower than 0.5 mol % are known in the literature.

Table 2. Optimization of the base/solvent system.



23 24 25

Entry	Solvent	Base	G.C Conversion [a]
1	Toluene	KOH	11
2	Toluene	NaOH	0
3	Toluene	LiOH	0
4	Toluene	CsOH	27
5	Toluene	K_3PO_4	0
6	Toluene	K_2CO_3	0
7	Dioxane	CsOH	20
8	Dioxane	K_3PO_4	0
9	DME	CsOH	0[b]
10	DME	K_3PO_4	11
11	Toluene	KO*t*Bu	22
12	Toluene	NaO*t*Bu	91[b]
13	Toluene	LiO*t*Bu	20[b]
14	Toluene	NaOtBu	>99[b,c] (80%)[d]
15	Toluene	KO*t*Am	0[e]
16	Isopropanol	LiO*t*Bu	0[e]
17	Isopropanol	KO*t*Am	0[e]
18	Isopropanol	KO*t*Bu	0[e]
19	Isopropanol	NaO*t*Bu	0[e]
20	Dioxane	LiO*t*Bu	15[b]
21	Dioxane	KO*t*Am	31
22	Dioxane	KO*t*Bu	51
23	Dioxane	NaO*t*Bu	73[b]
24	DME	KO*t*Am	0
25	DME	LiO*t*Bu	0[b]
26	DME	KO*t*Bu	16

27	DME	NaO*t*Bu	0[b]
28	Toluene	KO*t*Bu	0[f]
29	Toluene	NaO*t*Bu	0[b][f]

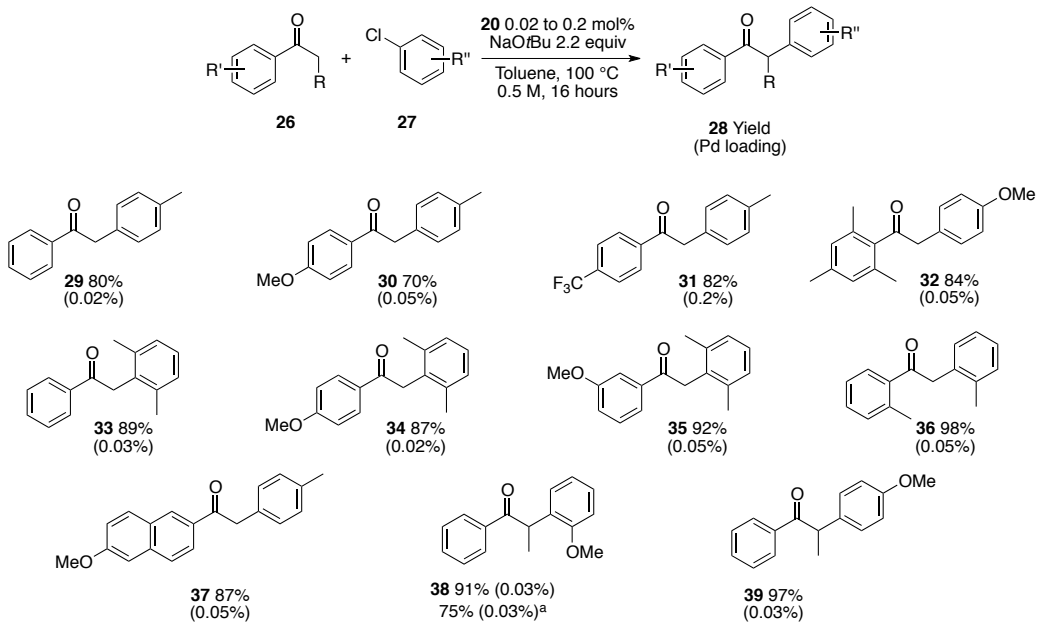
Conditions: 23 (0.7 mmol, 1.4 equiv), 4-Chlorotoluene (0.5 mmol, 1 equiv), base (1.1 mmol, 2.2 equiv), catalyst (0.01 mol%) in the indicated solvent (1 mL), 100°C, 16h. [a] Conversion of the 4-Chlorotoluene, as measured by GC; [b] no ketone detected by GC analysis; [c] 0.02 mol% catalyst; [d] isolated yield, average of 2 runs, after column chromatography; [e] the 4-chlorotoluene signal was not detected; [f] reaction performed in the absence of catalyst.

The optimization of the base/solvent system is crucial for CC reactions, as illustrated by Colacot.[3a,b] To this end, model CC reaction comprising acetophenone **23** and 4-chlorotoluene **24**, using catalyst **20** (0.01 mol%) was studied, systematically varying base and solvent. The use of carbonates, phosphates or hydroxides as bases generally resulted in poor conversion (see **Table 2**, entries **1-10**). The reason for unsuitability of inorganic bases lies mostly in their poor solubility in aprotic solvents, that makes the generation of the enolate slow. NaO*t*Bu, on the converse, provided significant conversion to the desired product in toluene and dioxane (91% and 73% respectively, entries **12** and **18**). Subtle change in the counterion of the *t*-butoxide, switching from sodium to other alkali metals, had a profound effect in the reactivity: employing LiO*t*Bu or KO*t*Bu, the conversion dropped significantly (entries **11-13**), both in toluene and dioxane. The correlation between the counterion used and the reaction outcome is not linear: the relative efficiencies of each base are influenced by the reaction solvent. Additionally, in some cases, the acetophenone signal was not detected in the GC (entries **9, 12, 13, 14, 17, 19, 21, 23**) despite it being used in excess; the signal of 4-chlorotoluene, moreover, was still present. Control experiments, using potassium- and sodium *t*-butoxide without pre-catalyst, proved that the side reaction leading to consumption of ketone is dependent on the counterion (entries **24 and 25**): KO*t*Bu does not promote the side reaction, leaving acetophenone untouched, whereas the ketone was completely consumed when NaO*t*Bu was present. All together, these results suggest that a subtle equilibrium between a side reaction (possibly aldol condensation, leading to degradation of the ketone) and the desired α-arylation, occurs. Sodium *t*-butoxide and toluene provided the optimum balance. An increase of the catalyst loading, from 0.01 to 0.02 mol%, lead to full conversion, and good yield, of the desired product. Other organic solvents (dioxane,

DME) used in conjunction with NaO*t*Bu or other organic bases afforded lower yields, the best conversion being 73% obtained with NaO*t*Bu in dioxane (entries **20-27**). The use of isopropanol (entries **16-19**) proved detrimental, as it lead to consumption of the haloarene without generation of the desired product. Such effect can be attributed to a transfer hydro-dehalogenation of the substrate, a well-known process under [Pd(NHC)] catalysis.[13]

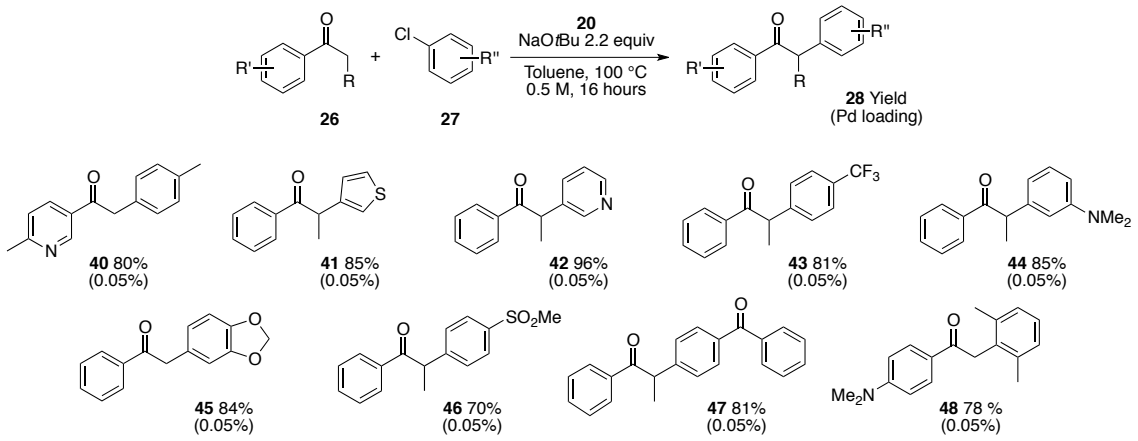
2.3 Scope of the protocol

Once the optimised reaction conditions were identified, we sought to study the scope of the methodology. First, the effect of the electronic properties of the ketone was investigated in the coupling with 4-chlorotoluene: the use of electron-rich 4-methoxyacetophenone resulted in good yield of the desired product when the catalyst loading was increased to 0.05 mol% (entry **30** 70% yield), while the electron-poor 4-(trifluoromethyl)-acetophenone required a 10-fold increase (0.5 mol% catalyst), with respect to acetophenone, to achieve full conversion and satisfactory yield (entry **31**, 82% yield). It has to be noted that electron-poor ketones, and especially methyl-ketones, are among the most challenging substrates for the α-arylation of ketones, because of the low nucleophilicity of the resulting enolate and the remarkable electrophilicity of the carbonyl moiety. Obtaining product **31** in 82% yield, at a catalyst loading which is still competitive with the current state of the art, is a remarkable result. The use of less reactive, electron-rich chloroarenes was also achieved (entry **32** 84% yield), as well as that of the sterically hindered 2,6-dimethylchlorobenzene (entries **33-34**, 89%, 87% and 92% yield respectively). Substitution at the 2- and 3- position of the acetophenone was also well tolerated (entries **36**, 98% yield, and entry **35**). An acetylnaphthalene derivative was also coupled successfully (entry **37**, 87% yield). Propiophenone proved a good substrate for the reaction, enabling the coupling with 2- and 4-chloroanisole in excellent yields at a catalyst loading of 0.03 mol% (entries **38-39**, 91% and 97% yield respectively). To test the suitability of the protocol in air, compound **38** was synthesised without the use of Schlenk or glovebox technique, still affording a satisfying yield of 75%.



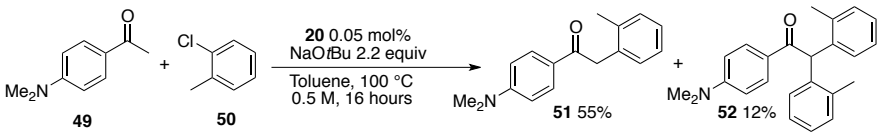
Scheme 2. Scope of the reaction: effect of the electronics and sterics of the coupling partners.

The excellent results showcased in **Scheme 1** prompted us to widen our investigation, testing compounds bearing pharmaceutically more relevant functional groups (see **Scheme 2**). For example, aromatic N-containing heterocycles were tolerated on both the ketone and the chloroarene (entries **40** and **42**, 80% and 96% yield respectively), and 3-chlorothiophene afforded good yield, too (entry **41**, 85% yield). A protected catechol derivative could be synthesised (entry **45**, 84% yield), using acetophenone as coupling partner. Chloroarenes bearing relatively base-sensitive functional groups, namely 4-chlorophenyl-sulfone and 4-chlorobenzophenone, also underwent the reaction smoothly (entries **46-47**, 70 and 81% yield respectively). The electron-poor 4-chloro-trifluorotoluene worked well (entry **43**, 81% yield), and coupling partners bearing a tertiary amine group were also well suited for this reaction (entries **44** and **48**, 85% and 78% yield respectively).



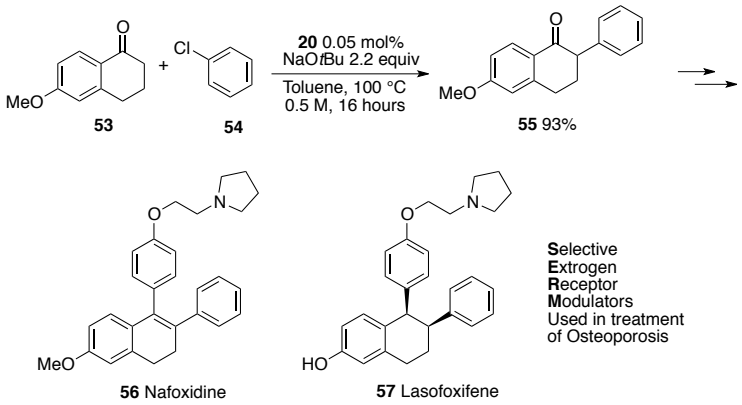
Scheme 3. Scope of the reaction: functional group tolerance.

The attempt to couple 4-dimethylamino-acetophenone **49** with less sterically hindered chloroarene, namely 2-chlorotoluene, highlighted a limit of this protocol: the reaction afforded a 5:1 mixture of mono- and di-arylated products (see **Scheme 3**). This was the only case in which we observed lack of complete selectivity towards mono-arylation. We postulated that the reason for this behaviour is the high electron-donating properties of the dimethylamine group: the enolate formed by deprotonation of the relatively bulky product **51** still retains enough nucleophilicity to overcome its steric hindrance, thus formed di-arylated product.



Scheme 3. Low selectivity in the arylation of the electron-rich acetophenone derivative

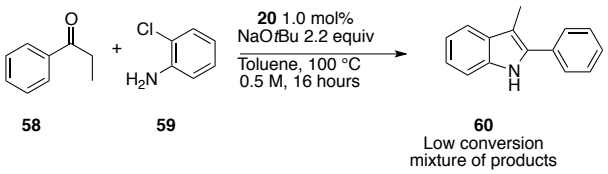
To verify the usefulness of the protocol, we sought to test it in the synthesis of compound **55**. This tetralone derivative is a known intermediate towards Nafoxidine **56** and Lasofoxifene **57**, selective estrogen receptor modulator; Lasofoxifene is currently in use for cancer treatment.[14] Performing the reaction under the optimised conditions, we obtain the product in 93% isolated yield using 0.05 mol% catalyst, half than the amount used by the authors for their patented procedure.[15]



Scheme 4. Synthesis of an intermediate towards SERMs drugs.

2.4 Conclusions and outcome

The development of more efficient Pd-catalysed cross couplings is a key area in modern organometallic and synthetic chemistry. The protocol discussed in this chapter is the first example known in the literature of general and high-yielding α-arylation of ketones at low catalyst loading (0.02-0.05 mol% for most of the examples). The methodology enables the coupling of coupling partners bearing functional groups relevant to medicinal chemistry applications (for example sulfone, amine and catechol derivatives). The good results obtained in the development of this project lead us into further studies on this and other related reactions: in particular, the development of [Pd(NHC)]-catalysed synthesis of heterocycles. In particular, during our work on this project, we attempted the direct coupling of an enolizable ketone and 2-chloroaniline, aiming at the direct one-pot synthesis of indole derivatives (see **Scheme 5**). Unfortunately, selective formation of the C–C bond between the α position of the ketone and the chloroarene was not possible: low conversion was observed at the GC, with a mixture of different compounds as products.



Scheme 5. Attempted application of the protocol to the synthesis of indoles.

Despite this poor preliminary result, we still pursued this objective, looking for ways to avoid side products. The results of our efforts in this project are described in the next chapter.

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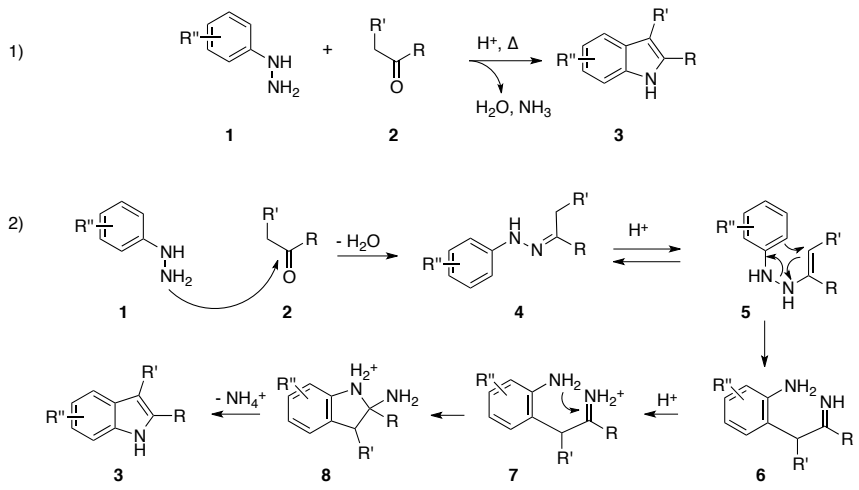
3 Synthesis of N-unprotected indoles and azaindoles *via* [Pd(NHC)] catalysed *α*-arylation of imines

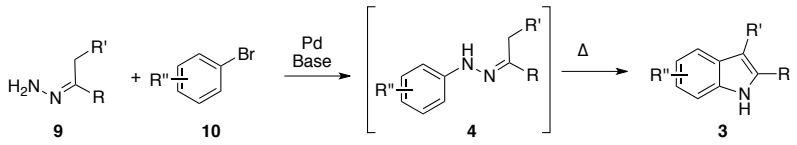
3.1 The importance of the indole scaffold in medicinal and material chemistry.

The vast majority of bioactive compounds, as well as many classes of functional materials, contain at least one heterocyclic core in their structure.[1] The great deal of attention that the synthesis and derivatisation of such molecular architectures has gained,[2] over a timeframe that spans for longer than a century, is hence not surprising. The number of medicines and naturally occurring compounds, containing at least one heterocyclic moiety, is countless, and cannot be summarised briefly. Although virtually any heterocyclic architecture has specific, valuable applications, the indole motif holds a key position in heterocyclic chemistry. Indole is considered the most widespread heterocycle in nature,[3] and its synthesis and functionalization has gathered an ever-increasing amount of attention by the whole synthetic community. The first reported synthetic method for indole derivatives dates back to the end of 19th century, and is still cited as a classic reaction in organic chemistry: the Fischer synthesis of indole.[4] This reaction takes place between an enolizable carbonyl compound (a ketone or an aldehyde) and a phenylhydrazine derivative under acid catalysis. Its key step is the C–C bond-forming 3,3-sigmatropic rearrangement of intermediate **5**, affording the imine **6**; this leads to the generation of the indole product after nucleophilic addition and ammonia elimination (see **Scheme 1**). The Fischer synthesis of indoles is nowadays still used for industrial synthesis of indole derivatives, and many variations, starting from different substrates or under different conditions, have been developed.[5]



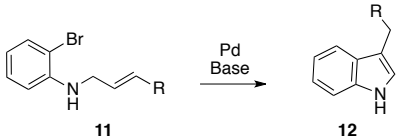
Scheme 1. Fischer's synthesis of indoles.[4]

A transition metal-catalysed approach to the Fischer N-arylhydrazone **4**, considered the key intermediate in this chemistry, was reported in 1999 by Buchwald (see **Scheme 2**): the Buchwald-Hartwig-type cross coupling between arylhydrazones and bromoarenes affords intermediate **4**, which results in formation of the desired indole product under heating. The authors proved the excellent flexibility of their method, allowing the synthesis of highly functionalised indole derivatives.[6]



Scheme 2. Buchwald's approach to Fischer's intermediate **4**.[6]

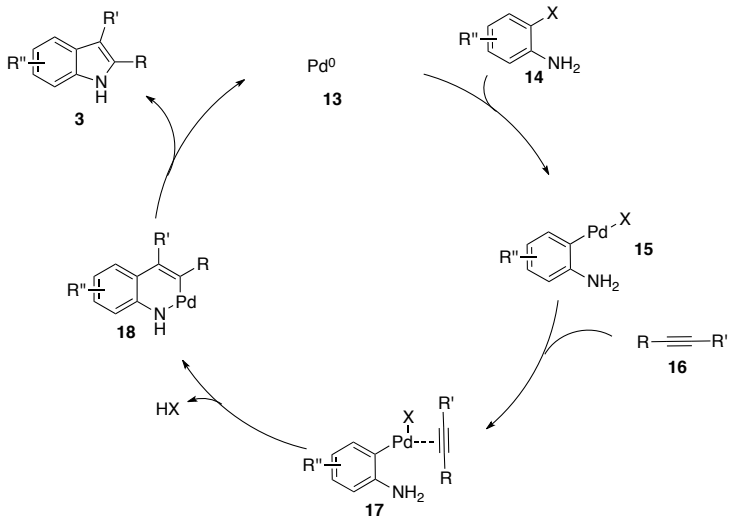
Other approaches relying on Pd catalysis have proven useful for the synthesis of the indole core. The field was actually pioneered by Hegedus, who reported the synthesis of indole derivatives *via* a Heck-type reaction of (2-Br-phenyl)-allylamines (see **Scheme 3**) between the late 1970z's the early 80's.[7] A closely related approach, also relying on a Heck-type reaction, was reported, by Mori and Ban.[8]



Scheme 3. Hegedus' synthesis of indoles.[7]

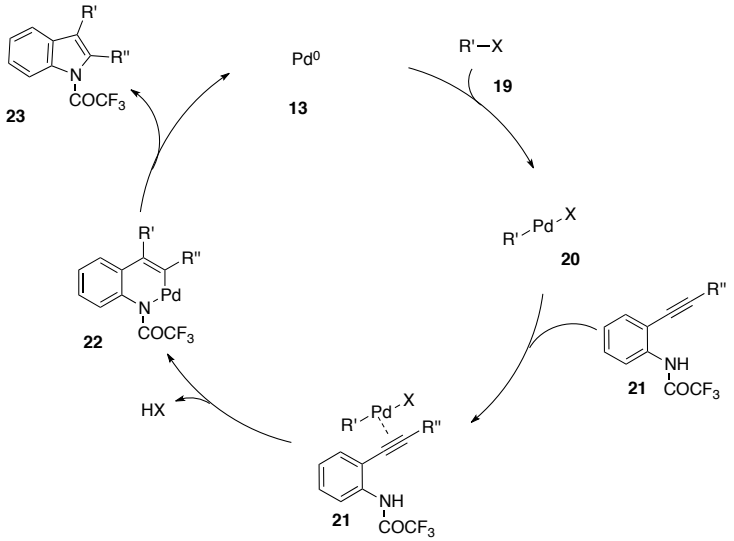
One decade later, Larock reported one of the most successful Pd-mediated synthesis of indole derivatives, starting from a *o*-haloaniline and an internal alkyne (see **Scheme 4**). This protocol, nowadays known with the name of its inventor, is based on the reaction

mechanism showed in **Scheme 4**: the Pd^0 catalytic species **13** undergoes oxidative addition on the Ar–X bond (an iodide in the figure), affording intermediate **15**, followed by carbopalladation of the internal alkyne, resulting in the formation of the cyclopalladated intermediate **18**. The desired product **3** and the catalytic species are formed in a reductive elimination step.[9]



Scheme 4. Larock's synthesis of indoles.[9]

A related protocol was reported one year later by Cacchi (see **Scheme 5**): the Pd^0 catalyst activates the C–X bond of an aryl electrophile, forming intermediate **20**, which then in turn activates the triple bond of substrate **21**. Carbopalladation to compound **22**, followed by reductive elimination, produce the desired product, regenerating the Pd^0 catalyst.[10]



Scheme 5. Cacchi's synthesis of indoles.[10]

These early reports have generated a vast amount of literature, to the extent that entire reviews have been devoted to the Pd-catalysed synthesis of indole-type heterocycles, allowing the preparation of highly functionalised derivatives.[11] Recently, new Pd-catalysed strategies for the synthesis of complex molecules have been developed, involving the α-arylation of ketones as key step. By interlocking the vast inventory of transformations known for carbonyl derivatives and the rapid developments of this CC reaction, these new synthetic pathways often provide elegant and creative routes for the synthesis of natural products and other bioactive compounds (for an exhaustive treatment of the topic, see **Section 1.4**). Molecular architectures such as indole, pyridine, isoquinoline, benzofuran and oxindole have been synthesized under α-arylation conditions. Once again, indole targets gather much of the attention devoted by researchers in the field. A summary of the retrosynthetic approaches adopted so far is given in **Fig. 1**.

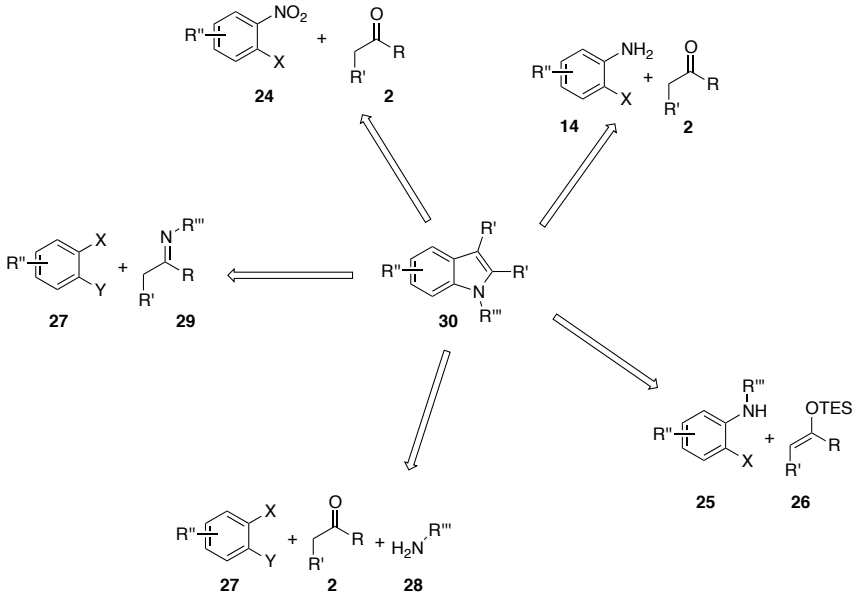
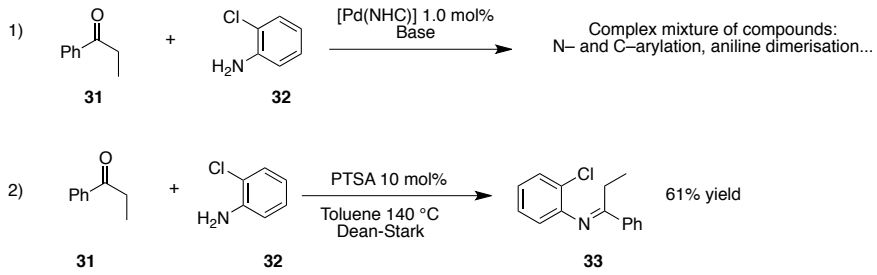


Figure 1. α-Arylative strategies towards polysubstituted indoles.

3.2 Optimisation of the [Pd(NHC)] catalysed reaction system for the intermolecular α-arylation of imines.

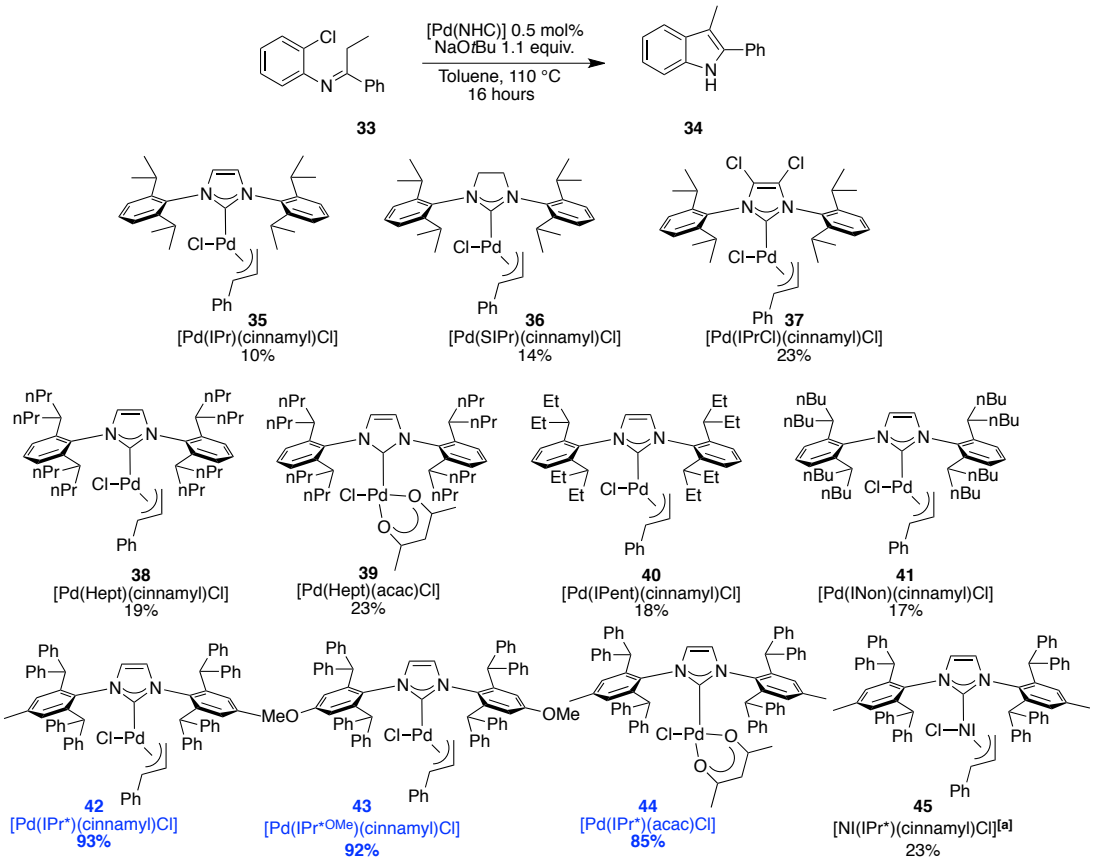
As showed in the previous chapter, our study of [Pd(NHC)] catalysts as catalysts for the α-arylation of ketones proved the remarkable effect that the new generation of "bulky yet flexible" N-heterocyclic carbenes have in the efficiency of the process. Attracted by the possibility to extend their utility in related synthetic processes, we decided to explore their activity in the synthesis of indoles. Unfortunately, the direct coupling of 2-chloroaniline and propiophenone, under the conditions reported in **Chapter 2**, lead to mixtures of coupled products, due to the low selectivity towards α-arylation and N-arylation (see **Scheme 6**, equation 1).[12] We envisaged that preforming the N–C bond, by pre-synthesizing the imine **33** by condensation, would possibly prevent side-reactions, thus overcoming this drawback (see **Scheme 6**, equation 2). Moreover, subjecting a pre-formed substrate to an intramolecular reaction brings the additional advantage to minimize the need for excess reagents, potentially improving the overall atom economy of the protocol. A similar protocol, converting the same type of substrates into indoles under Pd catalysis, was reported in 2005 by Lachance.[13] Despite this conceptually close precedent, we aimed at developing a method which would overcome the limitations of Lachance's: high catalyst loading (5 mol% $Pd(PPh_3)_4$, high temperature under microwave irradiation, lower yields when using chloroaniline derivatives. Moreover, these authors postulate a Heck-type reaction mechanism for their protocol, rather than a deprotonative α-arylation.



Scheme 6. Intermolecular approach to indoles and synthesis of imine **33**.

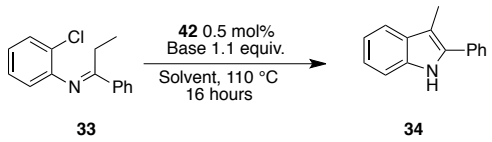
The imine **33** was subjected to the reaction conditions showed in **Chapter 2**, using different NHC-based pre-catalysts (see **Scheme 7**). We found that less sterically hindered ligand, such as IPr derivatives **35-37** and the ITent series **38-41**, provided poor conversion at a catalyst loading of 0.5 mol%. On the other hand, the flexible bulkiness

of IPr*-based ligands provided outstanding results: pre-catalysts **42** and **43**, bearing IPr* and IPr*^{OMe} ligands, respectively, afforded > 90% conversions to the desired product. Complex **44**, whose only difference to complex **42** is the substitution of the cinnamyl sacrificial ligand an acetylacetonate moiety, showed only slightly inferior reactivity, whereas changing the catalytic metal to Ni-based catalyst **45** resulted in very poor conversion, even at a relatively high catalyst loading of 5 mol%. The effect of the IPr*-derived ligands on Pd-catalysed processes is remarkable, and well documented in the literature.[14] The steric properties provided by this class of ligands have been useful in the study of highly unstable complexes based on Group 11 metals (especially Au).[15]



Scheme 7. Optimisation of the intramolecular approach towards indole **34**. Conditions: **33 (**0.25 mmol, 1.0 equivalents), NaO*t*Bu (0.28 mmol, 1.1 equivalents), catalyst (0.5 mol%) 0.125 M in toluene, 110°C, 16 hours. Conversion measured by G.C. [a] 5 mol% catalyst employed.

Table 1. Base-solvent optimisation



33 34

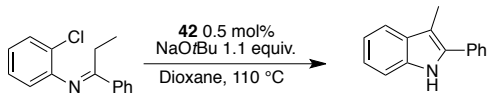
Entry	T °C	Base	Solvent	Conversion % [a]
1	110	LiO*t*Bu	Toluene	3
2	110	LiO*t*Bu	Dioxane	81
3	110	LiO*t*Bu	DME	95
4	110	NaO*t*Bu	Toluene	93
5	110	NaO*t*Bu	Dioxane	>99
6	110	NaO*t*Bu	DME	68
7	110	KO*t*Bu	Toluene	96
8	110	KO*t*Bu	Dioxane	16
9	110	KO*t*Bu	DME	33
10	110	NaHMDS	Toluene	70
11	110	NaHMDS	Dioxane	95
12	110	NaHMDS	DME	49
13	110	KO*t*Am	Toluene	4
14	110	KO*t*Am	Dioxane	14
15	110	KO*t*Am	DME	36
16	110	KOH	Toluene	25[b]
17	110	KOH	Dioxane	75 [b]
18	110	KOH	DME	34 [b]
19	110	K_3PO_4	Toluene	0
20	110	K_3PO_4	Dioxane	10
21	110	K_3PO_4	DME	7
22	80	NaO*t*Bu	Toluene	20
23	80	NaO*t*Bu	Dioxane	67
24	80	LiO*t*Bu	DME	33
25	80	KO*t*Bu	Toluene	10
26	80	NaHMDS	Dioxane	41

Conditions : 33 (0.25 mmol, 1.0 equivalents), base (0.28 mmol, 1.1 equivalents), **42** (0.5 mol%) 0.125 M in solvent, 80 or 110 °C, 16 hours. [a] Conversion measured by G.C. [b] 5 mol% catalyst employed.

After the identification of [Pd(IPr*)(cinnamyl)Cl] **42** as optimal catalyst for this reaction, we turned our attention towards the base/solvent system in which to perform the reaction. Three different solvents (toluene, 1,4-dioxane, and dimethoxyethane) were screened in combination with a wide range of organic and inorganic bases, namely tertiary alkoxides, NaHMDS (HMDS: hexamethyl-disilylamide) KOH, and

K_3PO_4 (See **Table 1**). Of the abovementioned bases, K_3PO_4 afforded very low conversion in all the solvents tested (entries **19-21**), while the employment of KOH resulted in higher conversion, but also a more complex reaction outcome, as many signals were detected in the GC track. Low conversions were also observed with KO*t*Am (tAm = *t*-amylate). On the converse, *t*-butoxides and NaHMDS provided high conversion (> 90%) in at least one of the solvents tested: NaO*t*Bu gave high conversion in both toluene and dioxane (entries **4** and **5**, 93% and >99% respectively), while LiO*t*Bu and KO*t*Bu gave a satisfactory result in DME and toluene, respectively (entries **3** and **7**, 95% and 96% respectively) and NaHMDS worked best in dioxane (entry **11**, 95%). To discriminate between these catalytic systems and find the most favourable reaction parameters, the abovementioned conditions affording conversion >90% were tested at a lower temperature, 80 °C, in order to comprare their relative efficiency (entries **22-26**). NaO*t*Bu in dioxane gave by far the higher conversion, 67% (entry **23**), whereas all the other conditions tested proved remarkably less performing (41% conversion or less).

Table 2. Fine tuning of the conditions.



33 **34**

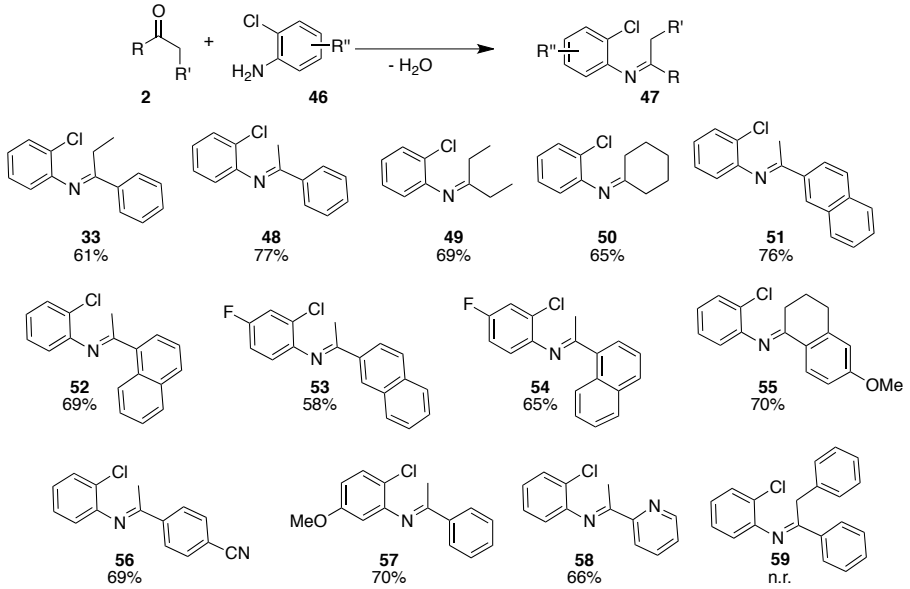
Entry	Pd loading (mol%)	Concentration	Reaction time (h)	Conversion %[a]
1	0.1	0.125 M	16	17
2	0.5	0.250 M	16	95
3	0.5	0.125 M	4	>99

33 (0.25 mmol, 1.0 equivalents), NaO*t*Bu (0.28 mmol, 1.1 equivalents), **42** (0.5 mol%) 0.125 or 0.250 M in solvent, 110°C, 4 or16 hours. [a] Conversion measured by G.C.

A further fine tuning of the reaction was performed (see **Table 2**): lowering the catalyst loading from 0.5 mol% to 0.1 mol% lead to a dramatic drop of conversion (17 %), while raising the concentration from 0.125 M to 0.250 M only slightly lowered the conversion to 95%; to our pleasure, the time needed for this reaction to reach completion was only 4 hours. The optimised conditions are summarised in entry **3**, **Table 2**: 0.5 mol% catalyst, 0.125 M concentration in dioxane, 1.1 equivalents of NaO*t*Bu at 110 °C. Although in some cases we were able to maintain these conditions, some other entries

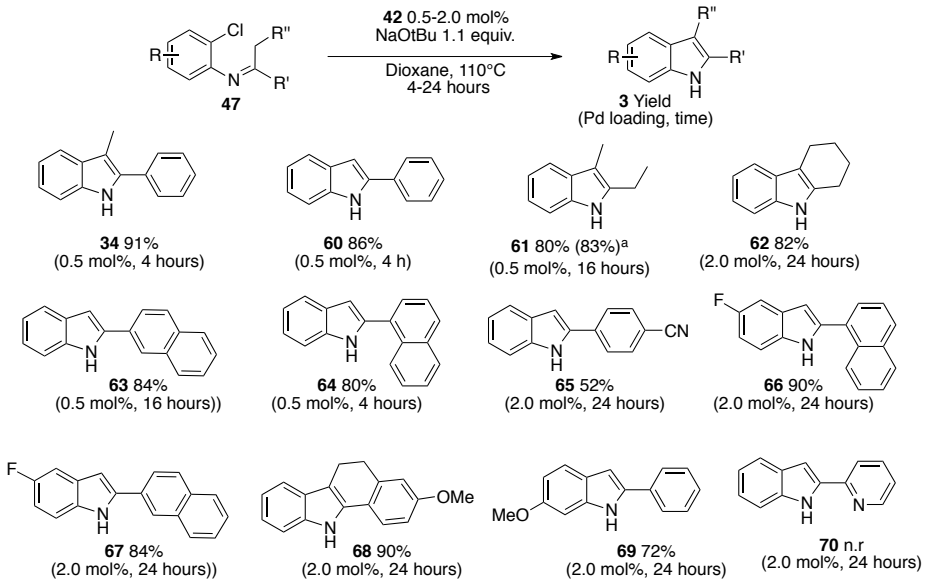
of the scope required increased reaction time and catalyst loading (*vide infra*). It has to be noticed that this protocol, even when the most forcing conditions were required (2 mol% catalyst, 24 hours), has remarkably low requirements: only a slight excess of base, a substrate/catalyst ratio of 50 or higher, and a single-component substrate, are needed to obtain the desired product, making it potentially suitable for scale-up.

3.3 Scope of the reaction



Scheme 8. Synthesis of imines **33** and **48-58**. For details on the protocol, see **Section 7.3**.

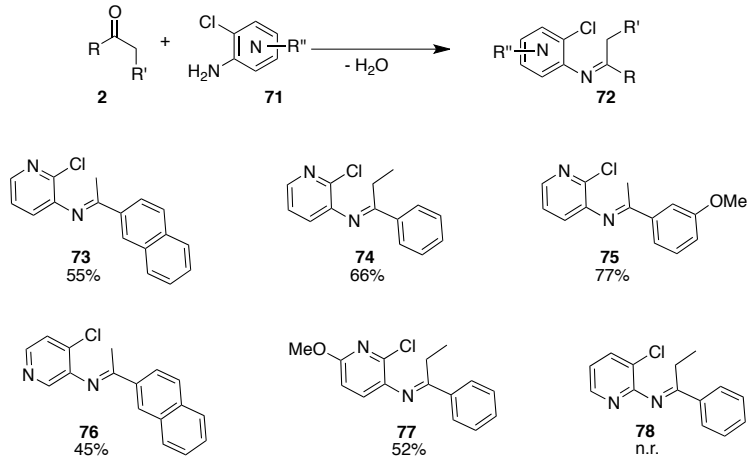
The imines **48-60** were synthesized by direct condensation of the selected ketone and chloroaniline, using basic alumina or *p*-toluensulphonic acid as catalyst, in the presence of excess of activated 3Å molecular sieves (see **Scheme 8**). The reaction generally proceeded smoothly, affording the desired imine in 61-77% yield after simple workup. Different ketones (dialkyl, aryl-alkyl, cyclic) could be used successfully, with the exception of deoxybenzoin (entry **59**). This is probably due to the large steric bulk associated with the contemporary presence of a phenyl and a benzyl groups at the carbonyl moiety. The imine substrates were then treated under the conditions previously optimised (see **Scheme 9**).



Scheme 9. Synthesis of indole derivatives. Imine **(**0.25 mmol, 1.0 equivalents), NaO*t*Bu (0.28 mmol, 1.1 equivalents), **42** (0.5 mol%) 0.250 M in dioxane, 110°C, 4, 16 or 24 hours. [a] Yield obtained in a gram-scale reaction.

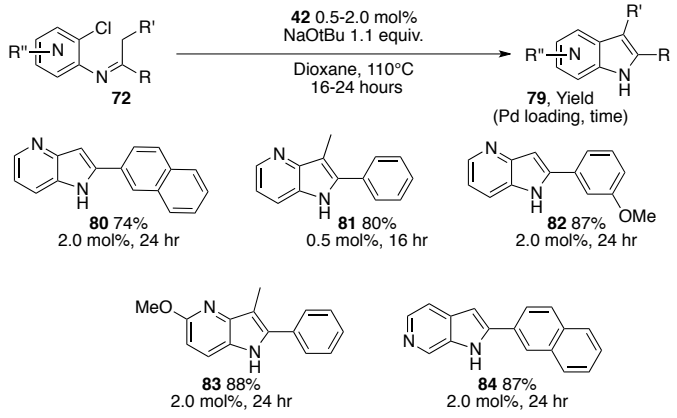
The product **34**, arising from model compound **33**, was isolated in 91% yield after column chromatography. The acetophenone-derived congener (entry **60**) also afforded good yield (86%) under the same reaction conditions. Dialkylketones proved suitable for this reaction: the pentanone derivative was obtained in a good 80% yield (entry **61)**, although in this case the reaction time had to be extended to 16 hours, whereas a cyclohexanone-derived (entry **62**) required to increase of the catalyst loading to 2%, and 24 hours time, to reach full conversion, affording 82%. Entries **63** and **64**, derived from 2- and 1-acetylnaphthalene respectively, were also obtained in good yields (84% the former, 80% the latter). The steric properties of the substituent in the 2-position of the indole have a remarkable effect on the reaction kinetics: while the less bulky 2-napthtalene moiety lead to slower reaction, requiring 16 hours to reach completion, the 1-naphthalene congener could be converted in only 4 hours. The fluorinated analogues of these compounds, (entries **65** and **66**), could also be synthesized using this protocol in good yields (84% and 90% respectively). The tetracyclic core **68**, which is known to have application in medicinal chemistry and optoelectronics,[16] was also obtained in 90% yield. The tolerance of our method to base-sensitive functional groups was proved by the successful synthesis of a nitrile-containing compound (entry **65**). The electronic deactivation introduced by the methoxy group in the *para*-position relative to the C–Cl bond could also be overcome easily, affording 72% yield of product **69**. The synthesis

of compound **61** could also be performed on a gram scale, showing the potential scalability of this protocol.



Scheme 10. Synthesis of imines **73-78**. For details on the protocol, see **Section 7.3**.

The wide substrate scope of this methodology prompted us to extend it to more challenging target compounds, such as azaindole derivatives. These compounds are of great interest in medicinal chemistry, and therefore a straightforward access to some of their functionalized congener would be of high value. Another set of imines, derived by various *o*-chloro-amino pyridine derivatives, was prepared and tested. The 2-chloro-3-aminopyridine derivatives **73-75** and **77** could easily be accessed by condensation, as well as the 3-amino-4-chloropyridine derivative **76**. On the converse, imine **78**, which would formally form from the condensation of the very electron-poor 2-amino-3-chloropyridine and propiophenone, could not be synthesized using this method. Our hypothesis is that the electronic deactivation of the NH_2 moiety leads to very poor reactivity.



Scheme 11. Synthesis of azaindole derivatives. Imine (0.25 mmol, 1.0 equivalents), NaO*t*Bu (0.28 mmol, 1.1 equivalents), 42 (0.5 mol%) 0.250 M in dioxane, 110°C, 16 or 24 hours.

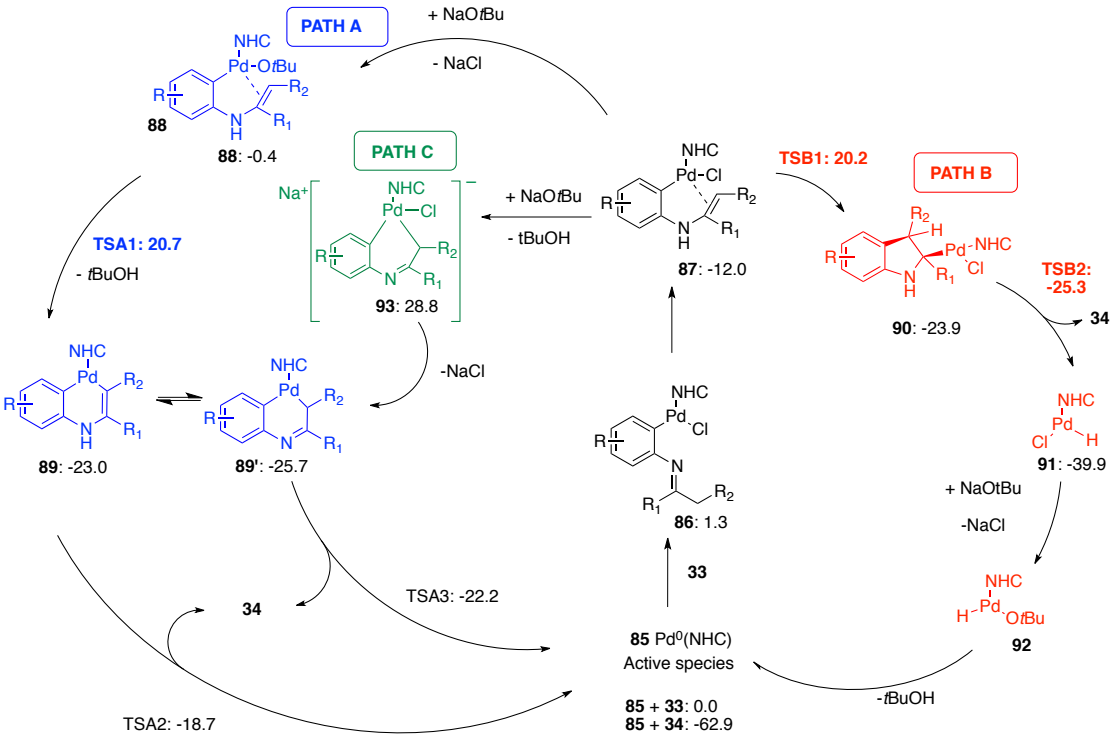
The 4-azaindole derivative **81**, which is the direct congener of the model target compound **34**, could be obtained in 80% isolated yield, using 0.5% mol catalyst loading for 16 hours. 2-acetylnaphthalene derivatives (entries **80** and **84**), respectively a 4- and 6-azaindole derivatives, were obtained in 74% and 87% isolated yield, respectively, under the harsher conditions (2 mol% catalyst, 24 hours). Under the same conditions, compounds **82** and **83**, bearing a methoxy substituent, were also obtained smoothly, both in 87% yield.

As it relies on a bench-stable pre-catalyst, without the need of carrying out any manipulation in the glovebox, this intramolecular synthesis of (aza)indole is remarkably practical. The commercial availability of 2-chloroanilines and enolizable ketones, from which the required substrates can be easily prepared, further highlights its utility.

3.4 Mechanistic studies

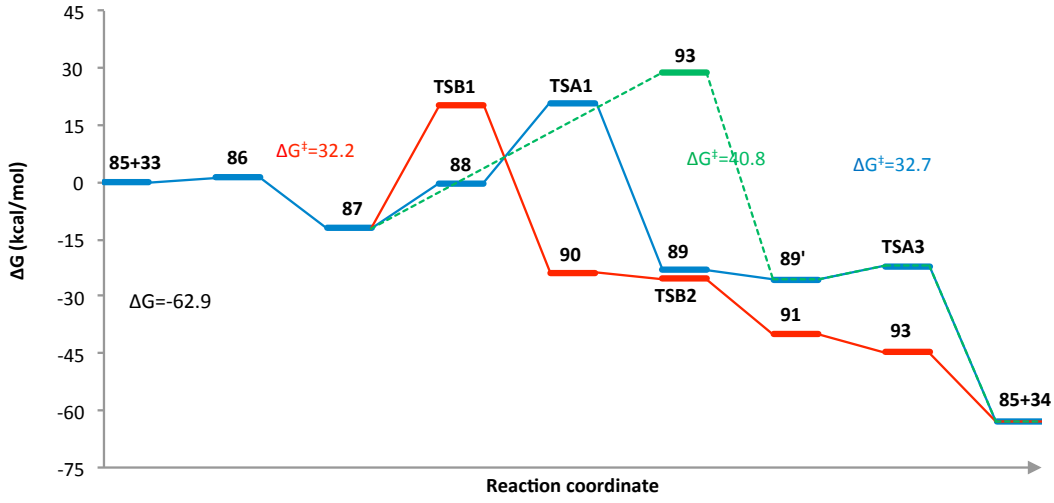
The synthetic utility of our protocol and its high efficiency lead us into more detailed studies of its mechanism. As mentioned above, Lachance postulated that, in a closely related protocol, based on [$Pd(PPh_3)_4$] as catalyst and triethylamine as base, a Heck-type reaction pathway would take place. Our initial assumption, however, was that a deprotonative, α-arylative cross coupling process, rather than a carbopalladation, is the preferred reaction path when NHCs are used as ligands.[17]

Computational experiments were carried out to distinguish between three possible reaction mechanisms (see **Scheme 12**): **Path A**, based on a deprotonative α-arylation of the imine followed by formation of the C–C bond *via* reductive elimination; **Path B**, based on the carbopalladation of the enamine double bond, followed by β-hydride elimination; and **Path C**, which is proposed to proceed through deprotonation of the imine without prior coordination of the *t*-butoxide anion on the Pd center, thus proceeding through to the ionic species **93**.



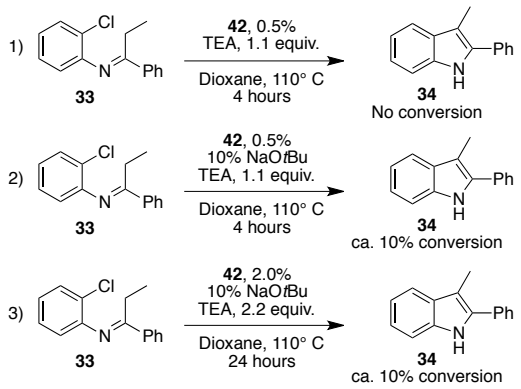
Scheme 12. The three proposed mechanisms for the reaction.

Despite several efforts, the current computational model did not discriminate between Path A and Path B, as the activation barriers of these two mechanisms were found to be very close in energy ($\Delta\Delta G^{\ddagger}$= 0.5 Kcal/mol), and the identification of the actual reaction mechanism by this mean was not doable. Path C, however, could be excluded, as the formation of the anionic species **92** would have too high an activation barrier to overcome it at the reaction conditions (see **Scheme 13**).



Scheme 13. Comparison between the three energy profiles of reactions Path A-C.

All the attempts to isolate any reaction intermediate proved unsuccessful. To overcome this ambiguity, we focused our attention towards the role of the base in Paths A and B. In the first case, as it really acts as a Brönsted base towards the imine α-carbon, its nature (and particularly its strength) is a key feature, influencing its activity. On the converse, the base acts as a simple proton sponge in Path B, quenching the HCl produced by reductive elimination of the [Pd(NHC)(H)Cl] complex **92**, implying a lower influence of its strength. Indeed, Mizoroki-Heck protocols normally involve the use of weak organic bases, such as triethylamine (TEA), as base additive (see **Scheme 14**). The profound influence of the base-solvent system, discussed above in relation to the data summarised in **Table 2**, already points toward a deprotonative mechanism.[18] We therefore postulate that a series of test reactions involving TEA as base would give us an additional indication on the mechanism of this process.



Scheme 14. Ruling out a Mizoroki-Heck pathway by assessing the role of the strong base.

When substituting NaO*t*Bu with TEA, the reaction completely stopped, and only starting material was recovered unreacted (see **Scheme 14**, equation 1). Such an effect of a weaker base could be due to the inability of the TEA base to activate the pre-catalyst, as a nucleophilic activation is required with the cinnamyl-based pre-catalyst **43**.[19] The reaction summarised in equation 2 substances this hypothesis: adding 10 mol% of NaO*t*Bu, the reaction does happen, although it stops when the strong *t*-butoxide base is consumed. Even with a higher catalyst loading and longer reaction time, TEA failed to convert the starting material into product, as highlighted in equation 3. Additional computational studies proved that TEA would enable the quenching of the HCl produced by a Mizoroki-Heck mechanism, whereas its basicity is insufficient to afford the imine enolate which is necessary to sustain a deprotonative

mechanism. This results provide an indication towards a deprotonative mechanism, however more detailed mechanistic studies would be required to identify the complete mechanism.

3.5 Conclusions and outcome.

An efficient and user-friendly synthetic access to indole and azaindole scaffolds was disclosed. As it requires only a small excess of base and a relatively low catalyst loading, it has great potential for applications on a larger scale. The choice of the ancillary ligand is crucial, as the strongly electron-donating, bulky IPr* N-heterocyclic carbene (and derivatives thereof) was required for obtaining highly active catalysts, thus highlighting the remarkable effect of the steric and electronic parameters of the ligand. Computational and experimental studies were performed to clarify the mechanism of such transformation, leading us to claim that a Mizoroki-Heck-type mechanism is unlikely, although the mechanism of the reaction is not clearly understood.

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4 Ni-catalysed α-arylation of ketones using chloroarenes as electrophiles

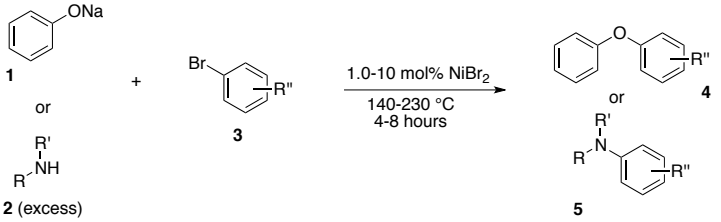
4.1 Nickel catalysis in C–C and C–X bond forming reactions

The use of rare transition metals in synthetic processes has caused increasing concerns in recent years:[1] their rarity in the earth crust had caused the price of some of them to increase to an economically unsustainable level. The synthetic community has tackled this situation by developing catalytic methods based on first row transition metals, most notably Fe, Co, Ni and Cu, which are far more readily available, significantly less expensive, and often less toxic than their heavier congeners.[2] The need for such protocols is compelling, in the perspective of a future world where the more used second- and third-row transition metals will be exceedingly expensive.

In the context of CC catalysis, in which Pd still holds a preferred position, the use of its first-row congener Ni is not uncommon. In fact, the first "modern" CC reported, the Kumada-Tamao-Corriu reaction, is based on Ni catalysis.[3] Moreover, Ni is a well-established industrial catalyst.[4] Ni shows catalytic properties that are closely related to those of Pd; its poor stability, however, often leads to inferior catalytic efficiency, namely lower turnover numbers, and narrower scope.[5] On the other hand, its high reactivity, due to the nucleophilicity of the Ni^0 moiety, opens the door to entirely new modes of action. The development of the activation of "inert" C–O bonds, namely those belonging to esters and ethers, and their subsequent use as electrophiles in CC chemistry, is one of the most interesting examples of this *renaissance*.[6] Moreover, on a molar basis, the market price of Pd is 1500 times higher than the price of Ni, making its economically appealing.[7] Many reviews have been published in the last few years, focusing on various aspects of Ni-catalysed CC chemistry.[8]

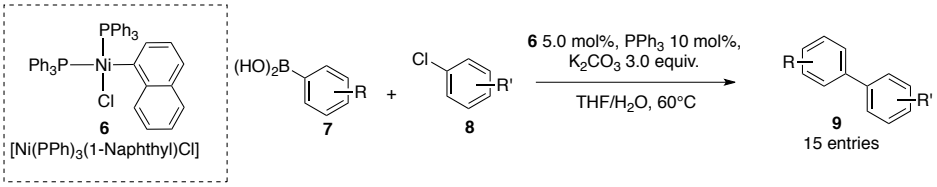
One early example of the use of Ni in CC chemistry was reported by Cramer, who studied "displacement reactions of aryl halides" with amines or phenoxides. In this case, simple aryl- or alkylphosphines, and ligand-free systems were employed, finding that $NiBr_2$ promoted the reaction, although it required very high temperatures (see **Scheme 1**).[9] The use of simple monodentate phosphine has been widely explored in the

late 70's. In a series of reports, Kochi showed the reactivity of different species, including paramagnetic Ni^{I} and Ni^{III} complexes, in some of the believed key steps of the catalytic cycle.[10]



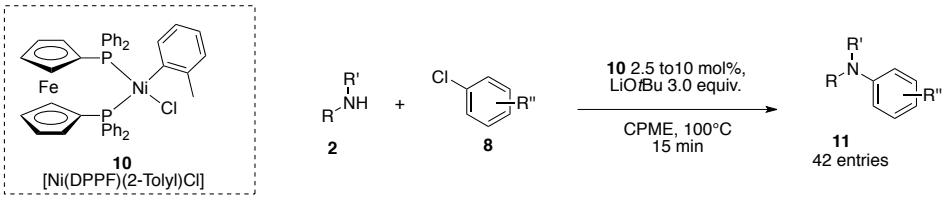
Scheme 1. Ni-catalysed C–X bond formation according to Cramer.[9]

More recently, complexes of formula $[Ni(PR_3)_2(Ar)Cl]$ were found to be competent catalysts for the Suzuki-Miyaura reaction (see **Scheme 2**).[11] As they are easily accessible and air stable, this class of catalysts has attracted the attention of many groups, whose studied their mechanism of action and their structure/activity relationships.[12]



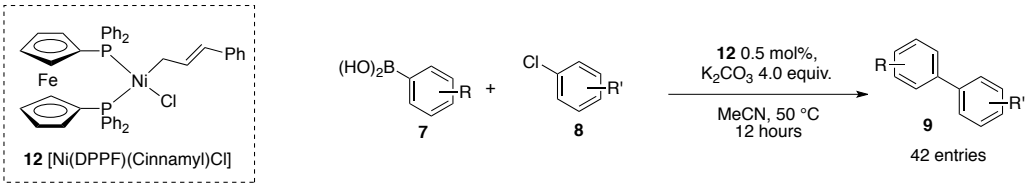
Scheme 2. $[Ni(PR_3)_2(Ar)Cl]$ complex as catalyst for the Suzuki Miyaura.[11]

Bidentate phosphines were found useful in typical CC reactions such as the Buchwald-Hartwig amination and the Suzuki-Miyaura biaryl synthesis.[13] Buchwald reported the use of $[Ni(COD)_2]$/DPPF in the amine arylation reaction, and, subsequently, an improved version of this catalyst was reported by the same author, enabling the coupling of a vast number of functionalised coupling partners (see **Scheme 3**).[14]



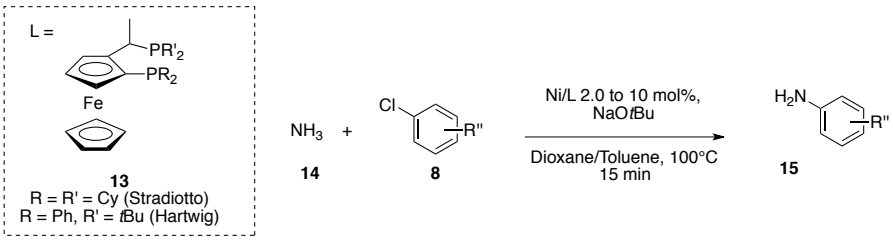
Scheme 3. [Ni(DPPF)]-catalysed Buchwald-Hartwig reaction according to Buchwald.[13]

In 2012, Hartwig reported the use of a single component, DPPF-based catalyst for the Suzuki-Miyaura CC. The protocol based on this catalyst shows high efficiency and a wide scope, and still represents the state of the art for the Ni-catalysed Suzuki-Miyaura reaction, in terms of functional group compatibility and catalytic efficiency (see **Scheme 4**).[15]



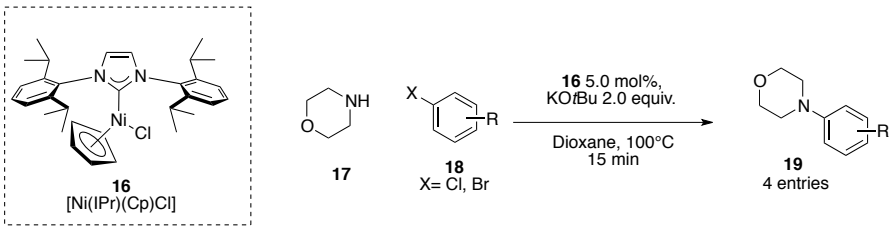
Scheme 4. [Ni(DPPF)]-catalysed Suzuki-Miyaura reaction according to Hartwig.[15]

More recently, Stradiotto and Hartwig almost contemporarily reported two closely related protocols for the mono-arylation of ammonia under Ni catalysis.[16] The ancillary ligands used belong to the JosiPhos family, chiral ferrocenyl-based bidentate phosphines (see **Scheme 5**). While both groups started their studies with the use of ammonia solution, they then focused on different possible alternative sources. While Stradiotto successfully focused on the direct use of ammonia gas, Hartwig's method enabled the use of ammonium salts as the ammonia sources.



Scheme 5. [Ni(JosiPhos)]-catalysed ammonia arylation according to Stradiotto and Buchwald.[16]

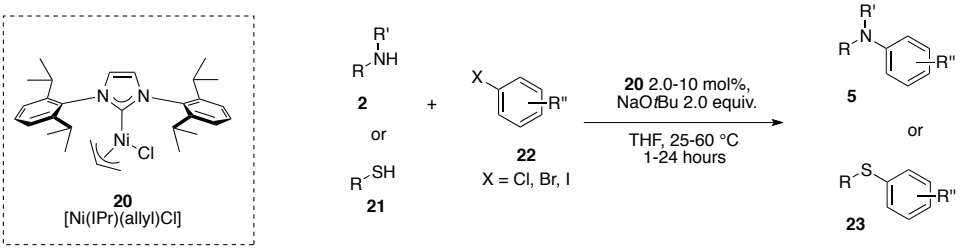
NHCs have proved highly effective as ancillary ligands in Ni catalysis. Monoligated NHC-Ni complexes showed activity in the Buchwald-Hartwig arylation.[17] Nolan reported that complexes of general formula [Ni(NHC)(Cp)Cl] (Cp = cyclopentadienyl) are active in the Buchwald-Hartwig CC (see **Scheme 6**).[18] The same complexes were also used for hydrothiolation reactions.[19]



Scheme 6. [Ni(NHC)]-catalysed Buchwald-Hartwig reaction according to Nolan.[17]

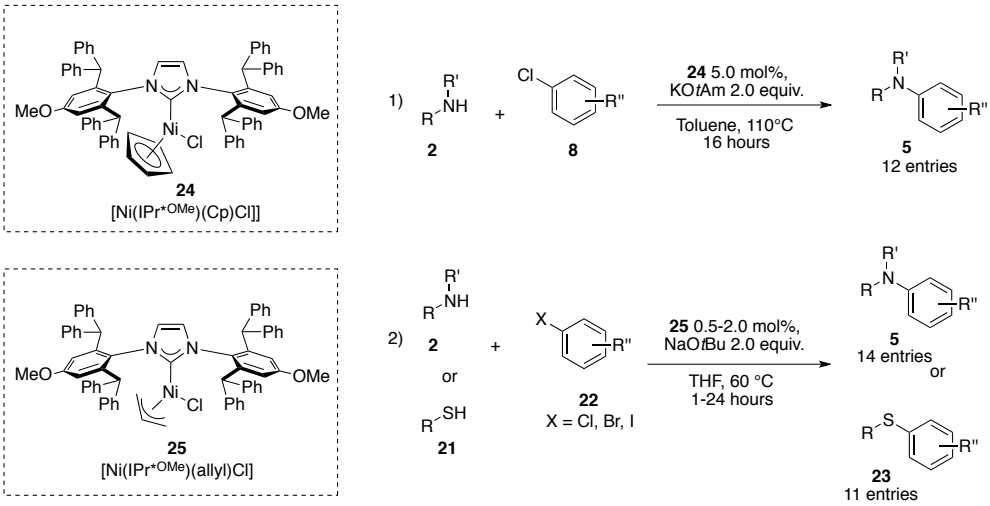
Subsequent works on complexes of formula [Ni(NHC)(allyl)Cl] **20** were reported by Nicasio and successfully applied as pre-catalysts for the Buchwald-Hartwig amination.[20] Chloroarenes could easily be coupled with both alkyl- and arylamines,

and the thiolation of bromo- and iodoarenes was also possible using these catalysts (see **Scheme 7**). As stated in the original report of such complexes, their air stability is very low, as they readily react with molecular oxygen.[21]



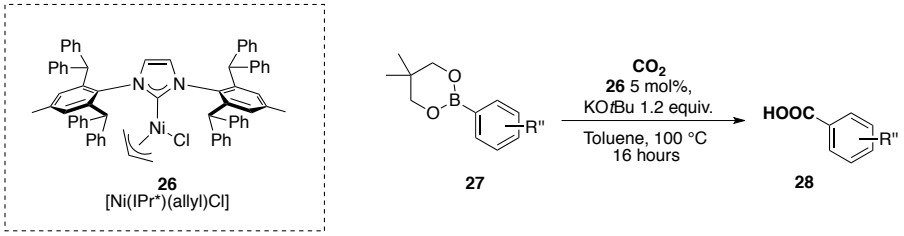
Scheme 7. [Ni(NHC)]-catalysed Buchwald-Hartwig and thiol arylation according to Nicasio.[18]

Recently, Nolan reported the greatly enhanced performance of the two aforementioned classes of NHC-containing pre-catalysts, when they are endowed with the bulkier IPr* and IPr*^{OMe} ligands. The improvement in catalytic activity was striking: the Cp-based catalysts, whose activity towards chloroarenes is usually very poor, could couple such electrophiles smoothly and in good yields. The allyl derivatives, on the other hand, enabled the arylation of amines and sulfides at catalyst loadings as low as 0.5-2.0 mol% (compare **Scheme 8** to the examples reported in **Scheme 6** and **7**).[22]



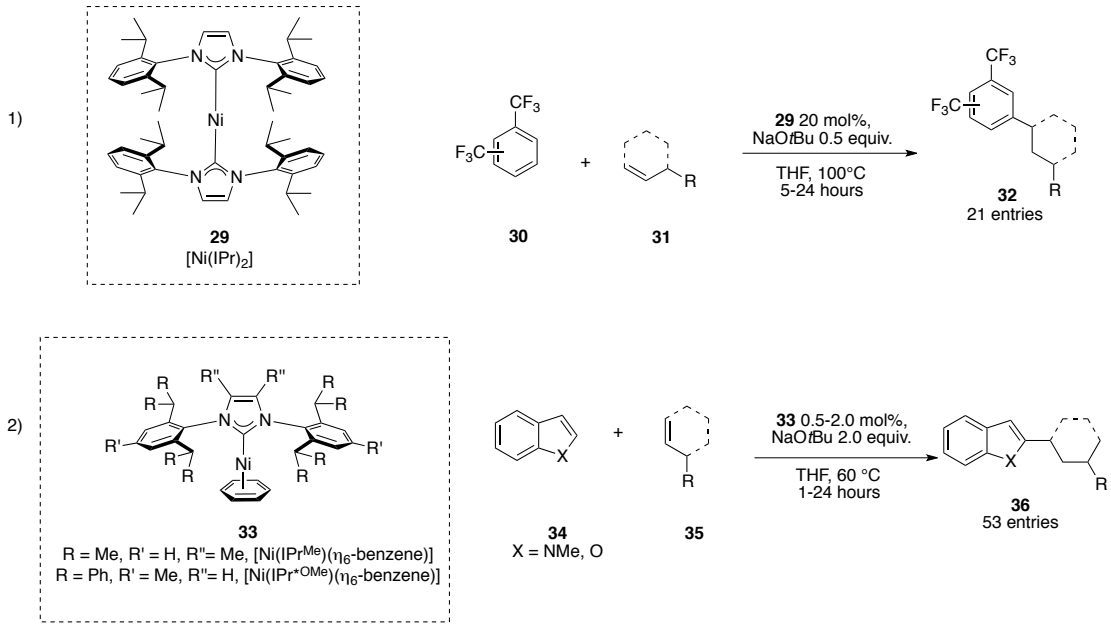
Scheme 8. The effect of bulky NHC ligands on the performances of Ni catalysts according to Nolan.[22]

The use of very bulky NHCs as ancillary ligands proved beneficial also in the case of other Ni-catalysed processes: Nolan showed that IPr*-based Ni complexes can perform the carboxylation of boronic esters, while less sterically hindered ligands provide substantially lower activity (see Scheme .[23]



Scheme 9. [Ni(NHC)]-catalysed carboxylation of boronates according to Nolan.[23]

The use of NHC ligands in catalysis was also tested in hydroarylation of alkenes by Hartwig and Nakao: depending on the nature of the substrate, IPr- or IPr*-derivatives provided high yields and selectivity (see **Scheme 10**).[24]

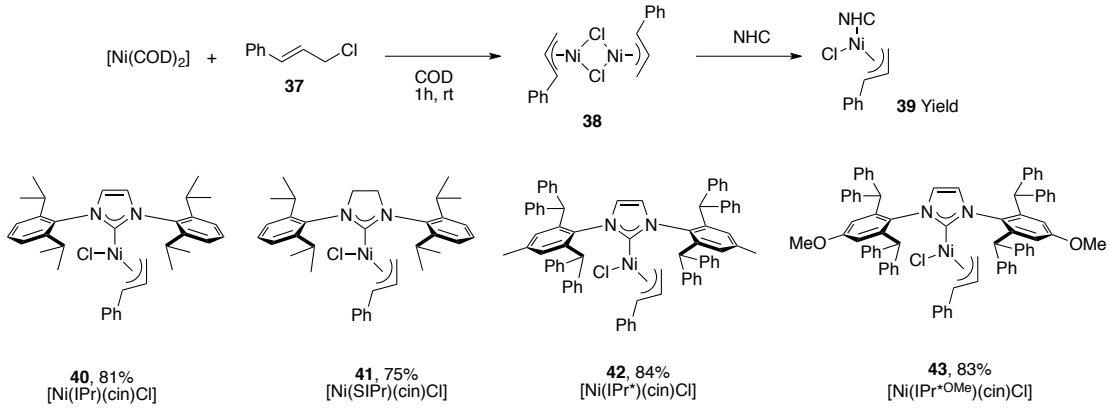


Scheme 10. [Ni(NHC)]-catalysed hydroarylation of alkenes according to Hartwig.

4.2 Synthesis of complexes of formula [Ni(NHC)(cinnamyl)Cl] and their evaluation in the α-arylation of ketones

Our initial aim was the development of a family complexes of formula [Ni(NHC)(cinnamyl)Cl]. The synthesis of such complexes proceeds smoothly under the conditions developed by Sigman.[21] Nolan reported a significant improvement in the catalytic performances of Pd pre-catalysts when the allyl throw-away ligand was substituted with the more sterically congested cinnamyl moiety;[25] this finding was later confirmed by further studies. Based on the protocol of Sigman, the [Ni(NHC)(cinnamyl)Cl] family of catalysts **39** was synthesised following a two step-procedure. A suspension of $[Ni(COD)_2]$ in COD was reacted with cinnamyl chloride, to

form the [Ni(cinnamyl)Cl]$_2$ dimer **38**. The dimer was then opened by addition of 1 equivalent of NHC ligand, affording the desired complexes **40**-**43** in very good yield.



Scheme 11. Synthesis of [Ni(NHC)(Cinnamyl)Cl] complexes **39**.

Crystal structures were obtained of the more sterically congested complexes **42** and **43**, bearing IPr* and IPr*^{OMe} as ancillary ligand, respectively (see **Figure 1**). The atom connectivity showed the expected complexes were formed. With these catalysts in hand, we proceeded screening their performances in the α-arylation of ketones.

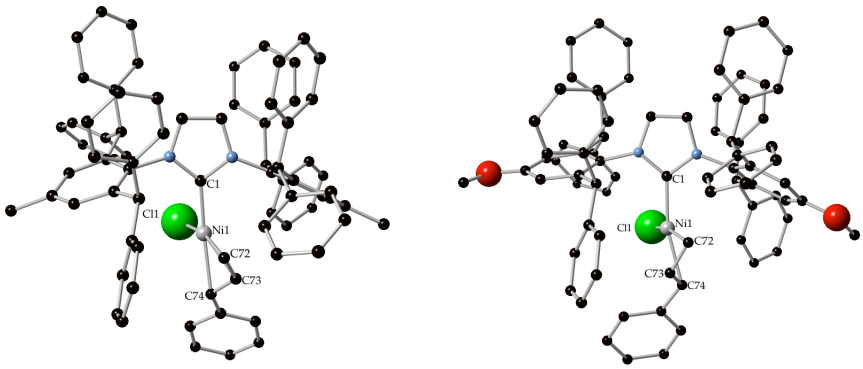
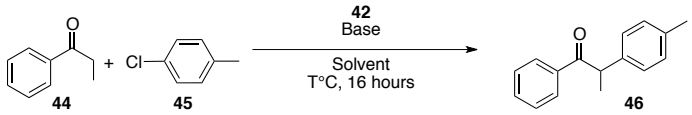


Figure 1. Crystal structures of complex **42** ([Ni(IPr*)(Cinnamyl)Cl], left-hand side) and **43** ([Ni(IPr*^{OMe})(Cinnamyl)Cl], right-hand side).

First, the base/solvent system was optimized using catalyst **42** (see **Table 1**) with 4-chlorotoluene **45** and propiophenone **44** as coupling partners. NaO*t*Bu was found to perform better than its Li- and K- congeners in THF, and its performances were even superior in toluene (entries **1-4**). An increase of temperature from 60 to 100 °C resulted in a slightly better conversion in toluene, which provided the best level of conversion when compared to other solvents (entries **5-7**). Increasing the amount of propiophenone from 1.2 to 2.0 equivalents, under the same conditions, led to a further improvement (entry **8**); lowering the temperature to 80°C resulted in full conversion

and 77% NMR yield (entry **9**); the temperature dependency may be due to thermal instability of the catalyst. An increase in the amount of base, from 1.5 to 2.0 equivalents sharply increased the NMR yield up to 92% (entry **11**). Using the same amount of other bases, on the converse, resulted in lower conversion (entries **12-15**).

Table 1. Identification of the base-solvent system.



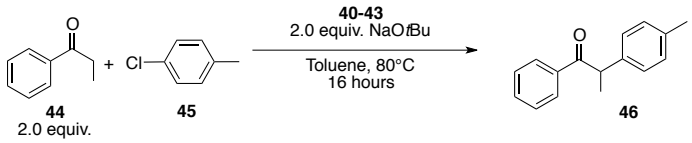
Entry	Equivalents 44	Base (equivalents)	Solvent	T (°C)	Conversion[a] (Yield)[b]
1	1.2	KO*t*Bu (1.5)	THF	60	0
2	1.2	NaO*t*Bu (1.5)	THF	60	30
3	1.2	LiO*t*Bu (1.5)	THF	60	20
4	1.2	NaO*t*Bu (1.5)	Toluene	60	56
5	1.2	NaO*t*Bu (1.5)	DME	100	17
6	1.2	NaO*t*Bu (1.5)	Toluene	100	80
7	1.2	NaO*t*Bu (1.5)	Dioxane	100	20
8	2.0	NaO*t*Bu (1.5)	Toluene	100	90
9	2.0	NaO*t*Bu (1.5)	Toluene	80	99 (77)
10	1.2	NaO*t*Bu (2.0)	Toluene	80	85
11	2.0	NaO*t*Bu (2.0)	Toluene	80	99 (92)
12	2.0	K_3PO_4 (2)	Toluene	80	0
13	2.0	KHMDS (2)	Toluene	80	60
14	2.0	NaHMDS (2)	Toluene	80	81
15	2.0	NaHMDS (2)	THF	80	71

Conditions: 44 (0.6 or 1.0 mmol, 1.2 or 2.0 equiv.), **45** (0.5 mmol, 1.0 equiv.), base (0.75 or 1.0 mmol, 1.5 or 2.0 equiv.), **42** (3.0 mol%) in the indicated solvent (2.0 mL), 60-100°C, 16h. [a] Conversion of **45**, as measured by GC; [b] NMR yield measure using dimethylmalonate as internal standard

The conditions summarized in entry **11** (2.0 equivalents of propiophenone, 2.0 equivalents of NaO*t*Bu, 0.25 M in toluene at 80 °C) were therefore adopted as the optimal. The following step we performed was the optimization of the ancillary ligand: complexes **40-43** were screened in the α-arylation reaction (see **Table 2**). While IPr- and

SIPr-based complexes **40** and **41** displayed low reactivity, affording 35% and 30% GC conversion respectively, their bulkier congeners **42** and **43** were able to fully convert the starting material to the desired product (entries **1-4**). At a catalyst loading of 1%, complex **42**, [Ni(IPr*)(cinnamyl)Cl], gave a slightly better result in comparison to its congener **43** (entries **5-6**). The optimized conditions, therefore, were the same as individuated in entry **11**, **Table 1**.

Table 2.



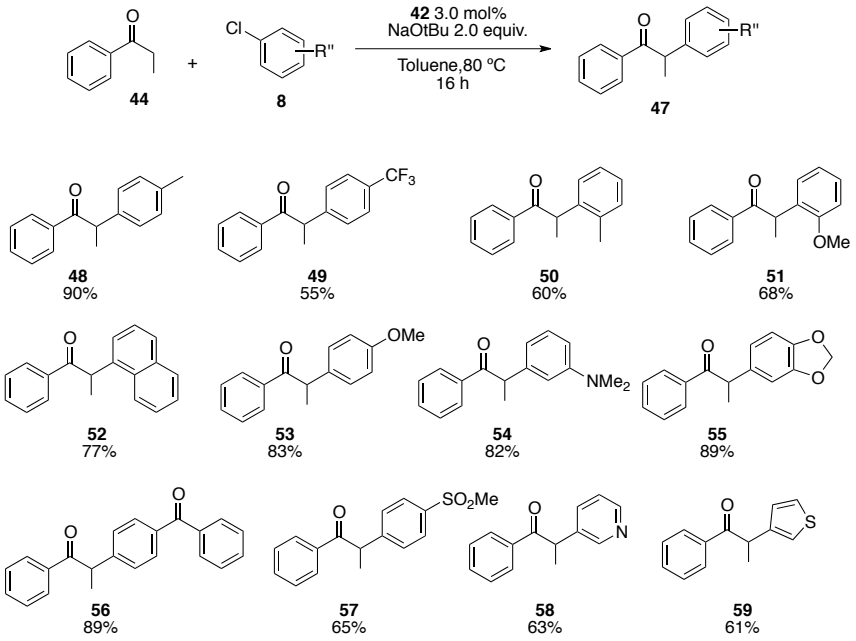
Entry	Catalyst (mol %)	Conversion[a]	Yield[b]
1	**40** (3 mol%)	35	-
2	**41** (3 mol%)	30	-
3	**42** (3 mol%)	99	92 (90)[c]
4	**43** (3 mol%)	99	89
5	**43** (1 mol%)	70	-
6	**42** (1 mol%)	80	-

Conditions: **44** (1.0 mmol, 2.0 equiv.), **45** (0.5 mmol, 1.0 equiv.), base (1.0 mmol, 2.0 equiv.), catalyst (3.0 mol%) in toluene (2.0 mL), 800°C, 16h. [a] Conversion of the 4-Chlorotoluene, as measured by GC; [b] NMR yield measure using dimethylmalonate as internal standard; [c] isolated yield.

4.3 Scope of the reaction

Having identified the optimal conditions, we proceeded with the exploration of the reaction scope. First, the effect of substituents on the chloroarene was investigated (see **Scheme 12**): we found that substitution with the electron-neutral methyl moiety with an electron-donating methoxy group still resulted in good yield (83%, entry **53**); on the contrary, the electron-withdrawing trifluoromethyl group had a detrimental effect, resulting in lower yield of desired product when bound to the electrophile (55%, entry **49**). Sterically hindered chloroarenes, such as 2-chlorotoluene and 2-chloroanisole, were suitable for the protocol, although also in this case the yields were moderate (60% and 68% respectively, entries **50** and **51**); the use of 1-chloronaphthalene, whose steric hinderance around the C–Cl bond is comparable to that of 2-chlorotoluene, provided a significantly better yield (77%, entry **52**). This improved performance can be explained

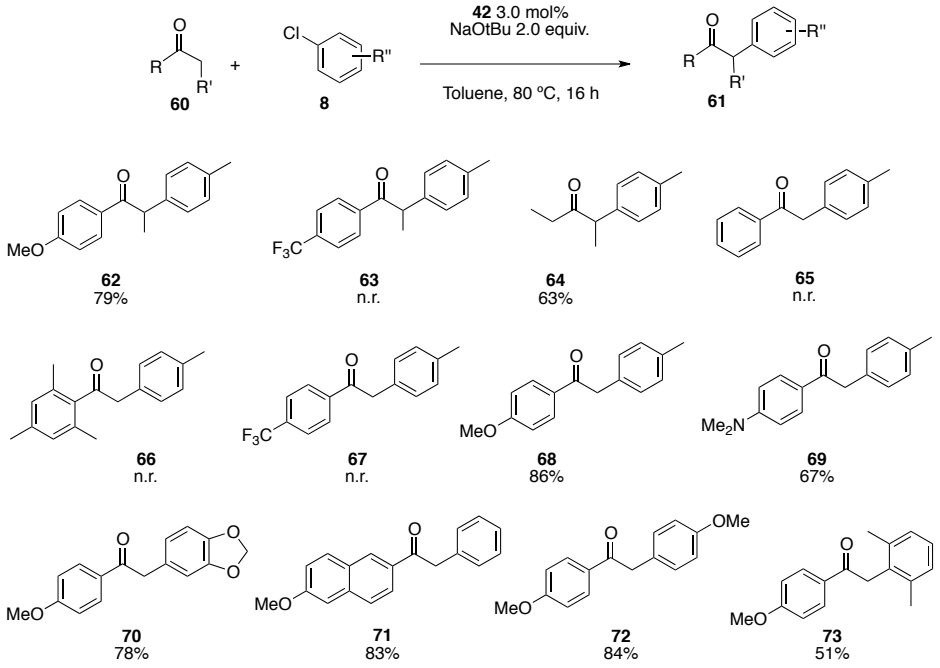
by the preference of Ni catalysts for polyciclyc aromatic electrophiles, probably due to the stabilisation of the Ni^0 catalytic species prior to the oxidative addition.[26] The protocol proved to enable the coupling of functionalised coupling partners: chloroarenes bearing tertiary amine (entry **54**), ketone (entry **55**) and protected catechol (entry **56**) moieties were successfully coupled with propiophenone in high to very high yields (82%, 89% and 89% respectively); the use of heterocyclic chloroarenes, such as 3-chloropyridine and 3-chlorothiophene, as well as a sulphone-containing one, was still possible although it resulted in moderate yields (63%, 61% and 65% respectively, entries **57**-**59**).



Scheme 12. Scope of the reaction: substitution on the chloroarene coupling partner.

The good results obtained in the coupling of differently functionalised chloroarenes led us to investigate the suitability of other ketones for this transformation (see **Scheme 13**). We found that the electron-rich 4-methoxypropriophenone could be coupled successfully with 4-chlorotoluene (79% yield, entry **62**), whereas the electron-poor 4-trifluoromethyl-propiophenone could not be coupled using our protocol, as its use resulted in no yield of the desired product (entry **63**). The use of a dialkylketone, namely 3-pentanone, was possible; to note, although the yield was only moderate, no diarylation was detected (63%, entry **64**). Moving our attention on the use of methylketone derivatives, we found that both electron-neutral and electron-poor compounds could not be coupled successfully (entries **65-67**). The use of these

compounds resulted in decomposition, as indicated by NMR analysis. On the other hand, electron-rich methylketones proved suitable: 4-methoxy- and 4-dimethylamino-derivatives could be reacted, and they afforded the desired product in good to moderate yield (86% and 67% yield respectively, entries **68**-**69**). 4-Methoxyacetophenone was successfully coupled also with 5-chlorobenzodioxol (78% yield, entry **70**), with 4-chloroanisole (84% yield, entry **72**) and with the very bulky 2,6-dimethylchlorobenzene (51% yield, entry **73**). This last result shows the great activity of our catalyst, as the use of *o*-disubstituted electrophiles is remarkably rare under Ni catalysis.[27] An electron-rich acetylnaphthalene could also be couple with good results (83% yield, entry **71**).



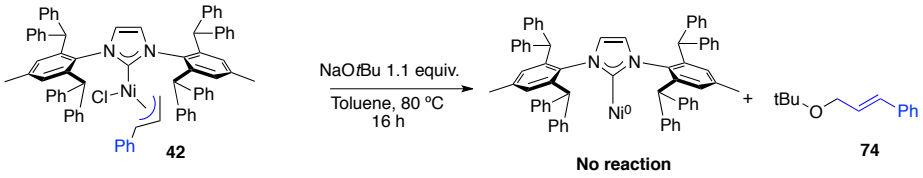
Scheme 13. Scope of the reaction: electronics and sterics of the ketone, very bulky chloroarenes.

The reaction scope provided by this protocol is very wide, while at the same time its great efficiency even under relatively mild conditions (3 mol% catalyst loading, 80 °C), makes it the state of the art for the coupling of haloarenes in the α-arylation of ketones.

4.4 Preliminary mechanistic studies

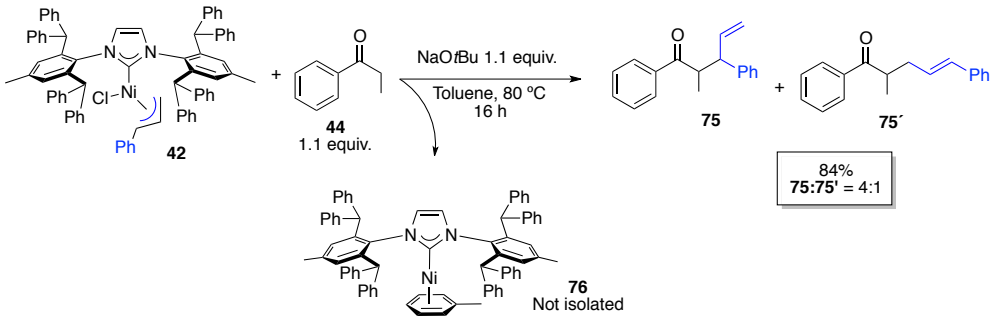
Given the unprecedented activity of complex **42** towards chloroarenes in the α-arylation of ketones, we focused our attention on the mode of action of such pre-catalyst. Chetcuti and Ritleng reported the activity of related catalysts, [Ni(NHC)(Cp)Cl], in this reaction (see section **1.2**), but did not manage to identify the

catalytically active species generated by these complexes.[28] The same author claimed that the activity of the Cp-based pre-catalysts towards chloroarenes was poor, whereas our catalyst showed excellent results when such substrates were used as substrates. We hypothesised that such a difference in activity might be due to the ability of the cinnamyl-bearing complexes to more easily release a monoligated Ni^0-NHC species upon nucleophilic activation, in a reaction similar to that displayed by their Pd congener.[25] We therefore tackled the mechanistic study of our pre-catalysts with the attempt to isolate the Ni^0 species generated by their activation (see **Scheme 14**). Our attempts to trap a complex containing the Ni^0-NHC moiety were unsuccessful. Treating complex **42** with 1.1 equivalents of NaO*t*Bu in toluene resulted in no formation of the postulated Ni^0 species, nor the activation by-product **74** (whose synthesis has been reported by Ogoshi through a different pathway)[29] was observed.



Scheme 14. Attempted isolation of the catalytically active species and of the activation by-product **74**.

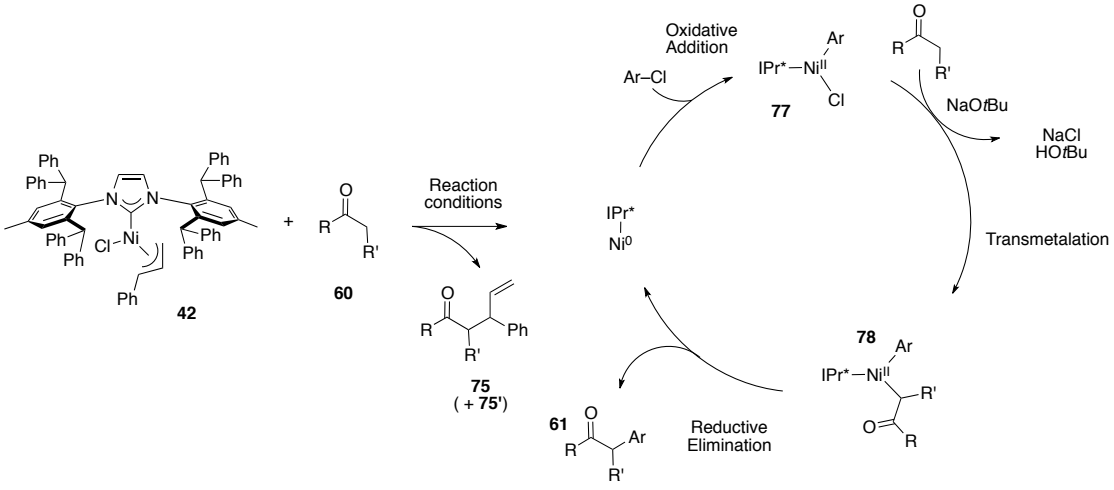
The treatment of complex **42** with propiophenone in basic conditions, however, provided some useful insights: a 3:1 mixture the α-allylation products **75** and **75′** were isolated from the reaction mixture in 84% isolated yield (combined).



Scheme 15. Isolation of activation by-products **75** and **75′**.

Although no Ni-containing species could be isolated from this mixture, the formation of these propiophenone derivatives hints at the formation of a [Ni(IPr*)(cinnamyl)(enolate)] species, from which the α-cinnamyl products **75** and **75′** are formed in a reductive elimination step, as observed by Hou using a related Pd-

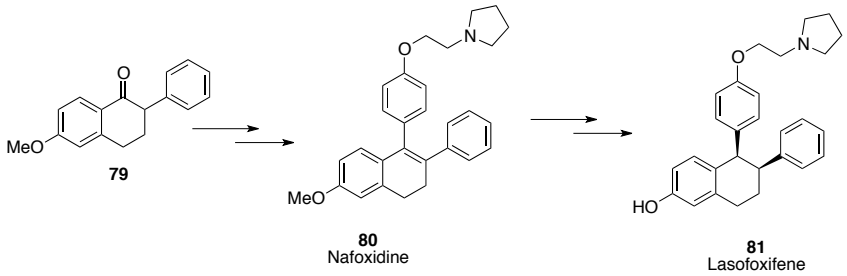
based catalyst;[30] a Ni^0-NHC is probably the other product of this reaction. Our attempts to trap such a species as an η^6-toluene adduct or by adding one equivalent of phosphine, forming the bis-ligated [Ni(NHC)(PR_3)] were unsuccessful. Nevertheless, the formation of products **75**-**75'**, together with the high catalytic activity observed with chloroarenes, strongly hint at a Pd-like, Ni^0 catalysed process (see **Scheme 16**).



Scheme 16. Proposed reaction mechanism.

4.5 Optimisation of the protocol for the synthesis an industrial intermediate

With a very efficient protocol in hand, we decided to further optimise for the synthesis of compound **79**. As showed in **Chapter 2**, compound **79** is an intermediate towards the Selective Estrogen Receptor Modulators (SERMs) Nafoxidine and Lasofoxifene.[31]

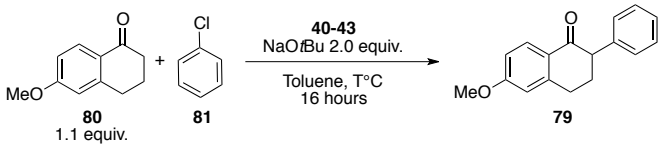


Scheme 17. Schematic synthetic pathways towards Nafoxidine and Lasofoxifene, with compound **79** as a key intermediate.

Our main goal in this further step of reaction optimisation was to enhance the overall reaction efficiency, more specifically its atom economy. For this reason, our first approach involved the lowering of the amount of ketone, with the double aim of reducing the waste of material and making the purification easier (see **Table 3**). We found that, contrarily to what we observed with propiophenone, 1.1 equivalents of 6-methoxytetralone were sufficient to fully convert the chlorobenzene starting material.

More interestingly, the optimal Ni pre-catalyst for this reaction was found to be complex **43**, bearing the IPr*^{OMe} ligand instead of IPr*. While reinforcing the importance of the ligand's steric bulk, this result further shows that subtle interactions between the ligand's eletronic properties and the nature of the substrates can determine the reaction outcome.

Table 3. Optimisation oft he ligand for the synthesis of **79**.



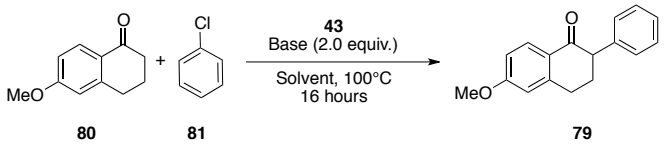
Entry	Pre-catalyst (mol%)	T °C	Conversion[a]
1	**40** (3)	80	0
2	**41** (3)	80	0
3	**42** (3)	80	99
4	**43** (3)	80	99
5	**42** (2)	80	66
6	**43** (2)	80	78
7	**43** (2)	100	>99

Conditions: **80** (0.28 mmol, 1.1 equiv), **81** (0.25 mmol, 1.0 equiv), NaO*t*Bu (0.5 mmol, 2.0 equiv), catalyst (2.0 or 3.0 mol%), in toluene (1 mL), 80 or 100°C, 16h. [a] Conversion of **81** was measured by GC.

With the finding that a different ancillary ligand, and a lower catalyst loading, could provide the desired product in good yield, a second round of optimisation was performed (see **Table 4**). The use of inorganic bases (Na_2CO_3, Cs_2CO_3, K_3PO_4) resulted in no reactivity (entries **2-4**). As we observed in the case of Pd catalysis (see **Chapters 2** and **3**), a complex interaction between the base and the solvent is observed: when switching between *t*-butoxide bases, we observed that Li was the best counterion in ethereal solvents (both dioxane and DME, entries **14-15**), and gave satisfying conversion in toluene too (entry **6**); K performed poorly both in toluene and ethers (entries **5**, **11-12**), but gave excellent conversion in DMF (entry **13**); NaO*t*Bu, however, provided good yield in DMF (entry **10**) and was the only base to provide full conversion, when used in combination with toluene (entry **1**).. The increase of the concentration in the reaction vessel, obtained by reducing the amount of solvent, did not affect the conversion rate, making the process more atom-economical as the solvent waste was halved (entry **19**). The reduction of the reaction time, however, was

detrimental, as it led to lower conversion (entry **20**), and further lowering the catalyst loading led to lower conversion (entry **21**).

Table 4. Optimisation of the base/solvent system fort he synthesis of **81**.

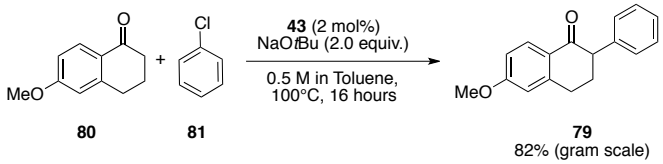


80 **81** **79**

Entry	Base	Solvent	mol% 43	Conc. (mol L^{-1})	Conversion[a]
1	NaO*t*Bu	Toluene	2	0.25	99
2	Na_2CO_3	Toluene	2	0.25	0
3	K_3PO_4	Toluene	2	0.25	0
4	Cs_2CO_3	Toluene	2	0.25	0
5	KO*t*Bu	Toluene	2	0.25	0
6	LiO*t*Bu	Toluene	2	0.25	72
7	NaOH	Toluene	2	0.25	15
8	NaO*t*Bu	Dioxane	2	0.25	46
9	NaO*t*Bu	DME	2	0.25	13
10	NaO*t*Bu	DMF	2	0.25	85
11	KO*t*Bu	Dioxane	2	0.25	0
12	KO*t*Bu	DME	2	0.25	0
13	KO*t*Bu	DMF	2	0.25	92
14	LiO*t*Bu	Dioxane	2	0.25	68
15	LiO*t*Bu	DME	2	0.25	74
16	LiO*t*Bu	DMF	2	0.25	25
17	NaOH	Dioxane	2	0.25	0
18	NaOH	DMF	2	0.25	0
19	NaO*t*Bu	Toluene	2	0.5	> 99
20	NaO*t*Bu	Toluene	2	0.5	90[b]
21	NaO*t*Bu	Toluene	1	0.5	75

Reaction conditions: 80 (0.28 mmol, 1.1 equiv), **81** (0.25 mmol, 1.0 equiv), NaO*t*Bu (0.5 mmol, 2.0 equiv), **43** (1.0 or 2.0 mol%), in solvent (1 mL), 100°C, 16 h. [a] Conversion of **81** was measured by GC; [b] reaction time 6 h.

The further optimised conditions lead to an isolated yield of the target compound of 82% on a gram scale reaction. The TON observed for the reaction, 41, is the highest ever registered for a Ni-catalysed ketone arylation. The improved reaction conditions (lower Ni loading, lower amount of solvent, only at a cost of a slight increase in temperature) show that the Ni-catalysed, industrial-scale protocols for the α-arylation of ketones, among other Ni-catalysed processes, can be developed.



Scheme 18. Gram-scale synthesis of **79**.

4.6 Conclusions and outcome

The substitution of Pd with Ni as catalyst for the α-arylation of ketones is part of the challenge towards the development a more sustainable and economically viable synthetic chemistry, both on the industrial and the laboratory scale. This chapter focuses the first Ni-catalysed protocol for the α-arylation using chloroarenes as electrophiles, at a catalyst loading that is comparable with the state of the art in the field. Its further optimization allowed the preparation of an industrially relevant intermediate, at the same time providing the most efficient example of Ni-catalysed the α-arylation of ketones to date. The steric and electronic properties of the NHC ancillary ligand proved crucial, as the very bulky ligands IPr* and IPr*^{OMe} clearly outperformed the more commonly used IPr and SIPr. The exploration of further [Ni(NHC)]-catalysed protocols for deprotonative couplings is discussed in the following chapter.

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Source: http://www.infomine.com/investment/metal-prices/, accessed 04-24-2017.

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5 Ni-catalysed arylation of benzylic C–H bonds for the synthesis of (diarylmethyl)amines.

5.1 (Diarylmethy)lamines

The diarylmethylamine motif is widespread in bioactive compounds,[1] with examples including the antidepressant Meclozine, the antihistamine Zyrtec (cetirizine), and the opioid **1**.[2] More recently, compounds bearing this pharmacophore have shown activity as antimicrobials,[3] antimalarials,[4] and in Alzheimer's disease treatment. Given their importance as bioactive compounds, the development of synthetic strategies towards (diarylmethyl)amines is an important area for synthetic chemists (see **Figure 1**).

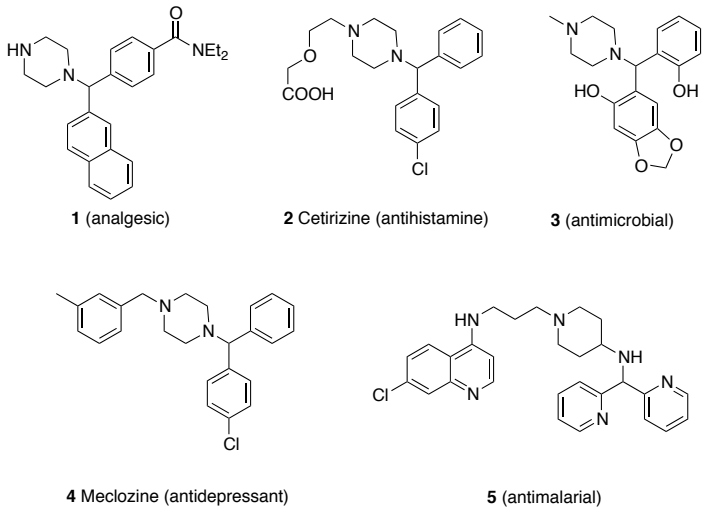
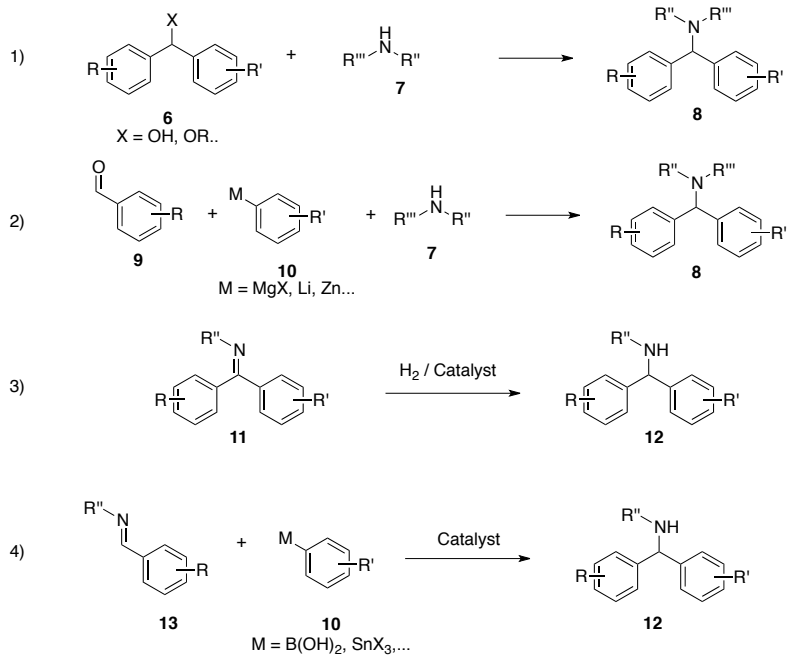


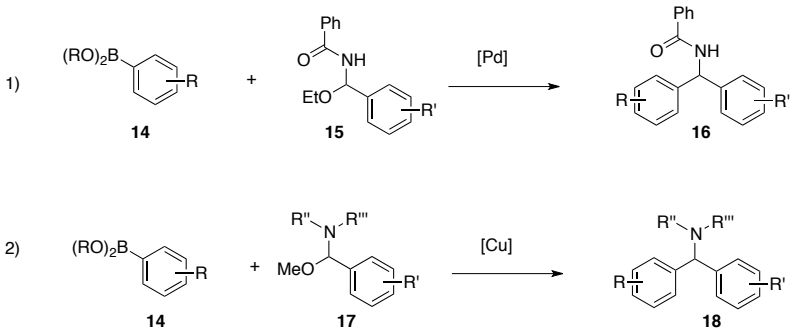
Figure 1. Examples of (diarylmethyl)amine derivatives.

Traditional synthetic chemistry approaches (see **Scheme 1**) involve the nucleophilic substitution of an amine on a benzhydril-derived electrophile (equation 1),[5] or the nucleophilic addition of organometallic reagents on a benzaldehyde-derived imine (equation 2).[6] Catalytic approaches towards this motif, namely the reduction of diarylketimines,[7] and the addition of a mild organometallic reagent to a benzaldehyde-derived imine,[8] are also known (equations 3 and 4).



Scheme 1. Common approaches towards the (diarylmethyl)amine scaffold.[5-8]

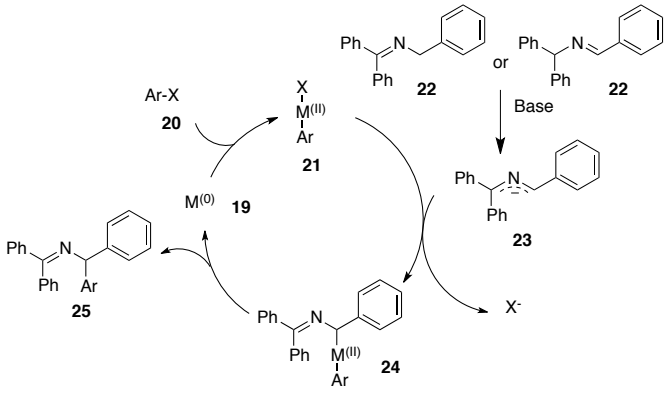
Less intuitive approaches have been designed, using transition metal catalysis: the activation of a *N*,*O*–acetals has been achieved, both under Pd and Cu catalysis (**Scheme 2**).[9]



Scheme 2. Pd- and Cu-catalysed, CC-like approaches towards (diarylmethyl)amines.[9]

The synthetic methods presented in **Schemes 2-3** doubtlessly represent a good selection of pathways to access the (diarylmethyl)amine moiety. However, each of these protocols presents drawbacks: often, lack of functional-group tolerance is observed, either because of the harsh conditions employed (highly nucleophilic organometallic reagents or strong acid catalysts) or because of the sensitivity of the catalyst employed towards certain functional groups leading to generally low yields or complex mixtures. Moreover, the substrates required for these approaches are often not commercially available.

The arylation of benzylamine-derived imines belongs to the deprotonative CC class of reactions, [10] and has proven useful for the synthesis of a large array of (diarylmethyl)amine derivatives, as shown in **Section 1.3.2**. Such a transformation is based on the deprotonation of a benzylic C–H bond belonging to a benzylamine derivative, and the subsequent coupling of the aza-allyl anion with a haloarene, generally under Pd catalysis (see **Scheme 3**). The development of a first-row metal-catalysed protocol would provide a more economically and environmentally sustainable alternative to the use of Pd, as explained in **Chapter 4**. For this reason, we saw the study of this C(sp^3)–H arylation under Ni catalysis as an intriguing and challenging area to showcase the ability of [Ni(NHC)]-based catalysts to perform CC chemistry with less reactive coupling partners.



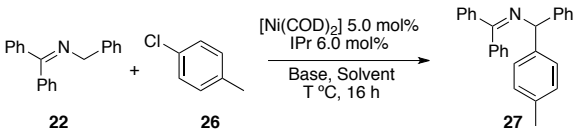
Scheme 3. The mechanism of the deprotonative CC of benzylamine-derived imines with haloarenes.

5.2 Optimisation of the reaction conditions

The examination of a reaction on the model compound **22** and 4-chlorotoluene **26** was the first step in our study (see **Table 1**). The effect of the base/solvent was first examined using a [Ni(COD)$_2$]/IPr **28** catalytic system. The choice to first test the base/solvent system was dictated by previous observations, reported by Walsh, that efficient and clean formation of the aza-allyl anion **23** is key in the reaction development.[10] Good conversion and NMR yields of the desired product were observed in toluene when potassium hexamethyldisilylamide (KHMDS) was used as base (entry **17**); KHMDS also provided quantitative conversion, but low NMR yield, in THF (48%, **entry 16**). Lower conversions were obtained with KHMDS in dioxane and dimethoxyethane (63% and 27% respectively, entries **14-15**). The other bases tested (Li- and NaHMDS and *t*-butoxides) gave no conversion to the desired product in all the

solvents screened (**entries 1-13**). The effect of the excess of base was also explored, leading us to the finding that amounts of base lower or higher than 2 equivalents led to a decrease in NMR yield (75% and 72%, respectively, **entries 18-19**). Increase in temperature, too, resulted in lower NMR yield (72%, **entry 20**).

Table 1. Optimisation of the base/solvent system.



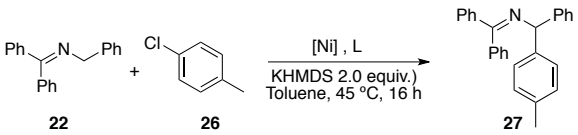
22 26 27

Entry	Base (equiv.)	Solvent	T° C	Conversion%[a] (yield) [b]
1	NaO*t*Bu (2.0)	Toluene	45	-
2	NaO*t*Bu (2.0)	Dioxane	45	-
3	NaO*t*Bu (2.0)	THF	45	-
5	KO*t*Bu (2.0)	Toluene	45	-
6	KO*t*Bu (2.0)	Dioxane	45	-
7	KO*t*Bu (2.0)	THF	45	-
8	NaHMDS (2.0)	Toluene	45	-
9	NaHMDS (2.0)	Dioxane	45	-
10	NaHMDS (2.0)	THF	45	-
11	LiHMDS (2.0)	Toluene	45	-
12	LiHMDS (2.0)	Dioxane	45	-
13	LiHMDS (2.0)	THF	45	-
14	KHMDS (2.0)	Dioxane	45	63
15	KHMDS (2.0)	DME	45	27
16	KHMDS (2.0)	THF	45	>95 (49)
17	KHMDS (2.0)	Toluene	45	>95 (81)
18	KHMDS (1.5)	Toluene	45	>95 (75)
19	KHMDS (2.5)	Toluene	45	>95 (72)
20	KHMDS (2.0)	Toluene	60	>95 (72)

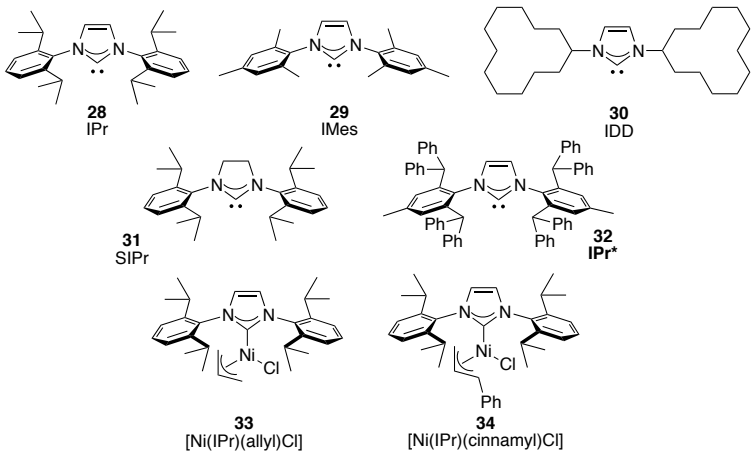
Conditions: 22 (0.5 mmol, 2.0 equiv), **26** (0.25 mmol, 1.0 equiv), base (1.0 mmol, 2.0 equiv), [Ni(COD)$_2$] (5. mol%), IPr (6.0 mol%) in the indicated solvent (2.5 mL), 45 or 60 °C, 16h. [a] Conversion of the 4-Chlorotoluene, as measured by GC; [b] Yield calculated by NMR analysis using dimethylmalonate as internal standard chromatography.

With an efficient base/solvent system in hand, we studied the influence of the ancillary ligand in the transformation (see **Table 2**): compared to the "medium-size" IPr NHC (entry **1**), the use of the less sterically hindered ligands IMes **29** and IDD **30** resulted in poor or no conversion (entries **5**-**6**), whereas the closely related SIPr ligand (entry **2**) provided good conversion, but only moderate NMR yield. The very bulky IPr* ligand, that usually gives the best performances when employed in CC chemistry (and especially under Ni catalysis), resulted as well in decreased yield compared to IPr (entry **3**). As IPr was identified as the optimal ligand, we tested well-defined pre-catalysts **33** and **34**, endowed with such ligand. Contrarily to the previous cases of [Ni(NHC)] catalysed reactions, both these pre-catalysts proved less efficient compared to the *in situ* prepared [Ni(COD)$_2$]/free IPr system (entries **7-8**). This drop in efficiency might be attributed to the activation step of the allyl- and cinnamyl- moieties when a sterically bulky, poorly nucleophilic 2-azallyl anion is used to generate the active Ni^0 species. It is interesting, however, to notice that the cinnamyl-base complex **34** provided remarkably higher conversion. The concentration could be increased to 0.17 M (83%, **entry 10**), but further increase led to erosion of the yield (53%, entry **9**). A metal/ligand ratio of 1:2 was found to improve the catalytic performance (93%, **entry 12**), whereas the addition of one more equivalent of ligand compared to the metal completely switched off the reaction (entry **13**). The dramatic effect of the excess ligand on the reactivity is surprising, and is discussed in **Section 5.4** together with other findings on the mechanism. Other Ni sources, namely [Ni(DME)Cl$_2$] and [Ni(acac)$_2$], proved ineffective (entries **14**-**15**).

Table 2.



Entry	Ni source (mol%)	L (mol%)	Conc. (mol L^{-1})	Conversion[a] (yield)[b]
1	[Ni(COD)$_2$] (5)	IPr 6%	0.10	>95 (81)
2	[Ni(COD)$_2$] (5)	SIPr 6%	0.10	94 (65)
3	[Ni(COD)$_2$] (5)	IPr* 6%	0.10	>95 (60)
5	[Ni(COD)$_2$] (5)	IDD 6%	0.10	-
6	[Ni(COD)$_2$] (5)	IMes 6%	0.10	24
7	**34** 5%	-	0.10	>95 (70)
8	**33** 5%	-	0.10	70 (45)
9	[Ni(COD)$_2$] (5)	IPr 6%	0.25	>95 (53)
10	[Ni(COD)$_2$] (5)	IPr 6%	0.17	>95 (85)
11	[Ni(COD)$_2$] (2.5)	IPr 3%	0.17	>95 (72)
12	[Ni(COD)$_2$] (5%)	IPr 10%	0.17	>95 (93)
13	[Ni(COD)$_2$] (5%)	IPr 15%	0.17	-
14	[Ni(acac)$_2$] (5%)	IPr 10%	0.17	traces
15	[Ni(DME)Cl$_2$] (5%)	IPr 10%	0.17	traces

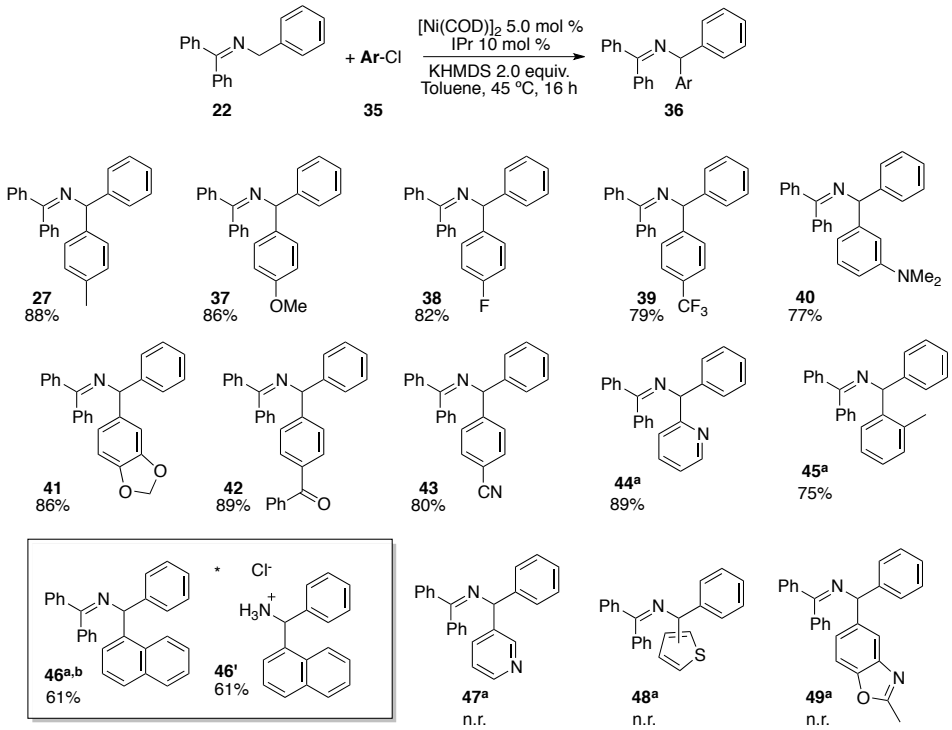


Conditions: 22 (0.5 mmol, 2.0 equiv), **26** (0.25 mmol, 1.0 equiv), KHMDS (1.0 mmol, 2.0 equiv), Ni source (2.5 or 5.0 mol%), ligand (3 to 10 mol%) toluene (1.0 to 2.5 mL), 60 °C, 16h. [a] Conversion of the 4-Chlorotoluene, as measured by GC; [b] Yield calculated by NMR analysis using dimethylmalonate as internal standard chromatography.

The transformation takes place at low temperature, which makes it possible to avoid the formation of mixtures of isomers, contrarily to what observed by Yorimitsu and Oshima in their early reports.[11] Compared to previous protocols reported by Walsh, our system did not require the slow addition of the base, thus rendering this methodology more user-friendly.[10] The conditions summarised in **Table 2**, entry **12** were therefore adopted as optimal, as they lead to 88% isolated yield of compound **27**.

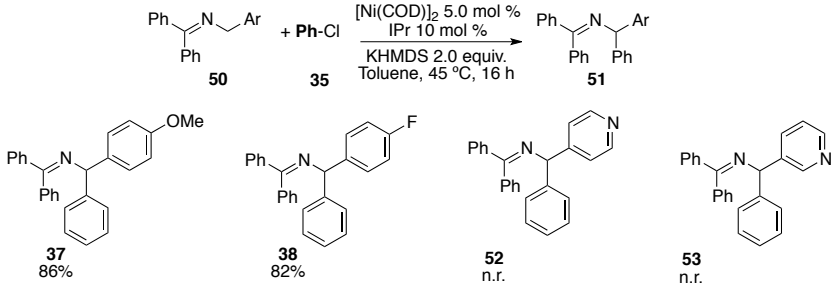
5.3 Scope and limitations

Once we had established the conditions for our methodology, we investigated the generality of our method by varying the substitution pattern of the chloroarene reactants for the coupling with the imine **22** (see **Scheme 4**). Both the electron-donating 4-methoxy substituent, as well as the electron-withdrawing trifluoromethyl group, led to high yields of the desired products (86% and 79% yield respectively, entries **37** and **39**). 4-fluorochlorobenzene could also be coupled smoothly (82%, entry **38**). Functionalised aryl chlorides, bearing functional groups such as amines (77%, entry **40**), benzodioxole (86%, entry **41**) and relatively base-sensitive ketone and nitrile derivatives (89 and 80% respectively, entries **42-43**) were also considered, and they were found to afford good to very good yields of the desired products. 2-chloropyridine was also successfully coupled in high yield (89%, entry **44**), although it required a slight increase of the catalyst loading, from 5 to 7.5 mol% to achieve full conversion. The same increase was necessary also for the coupling of sterically encumbered chloroarenes, namely 2-chlorotoluene and 1-chloronaphthalene, obtaining full conversion and fair yield (75% and 61% respectively, entries **45-46**). Compound **46** could not be isolated as such, because an impurity co-eluted with it: the yield was therefore calculated after the hydrolysis of the imine and isolation of the free amine **46'**. The good yields obtained using bulky chloroarenes are unprecedented, as they represent challenging substrates even for the Pd-catalysed protocols reported by Walsh.[10] Scheme **4** also shows products that could not be synthesised by means of this protocol: 2- and 3-chlorothiophene and 5-chlorobenzoxazole could not be coupled under the reaction conditions (entries **48-49**); 3-chloropyridine, too, proved unsuitable, in striking opposition to the good yield provided by the 2-chloropyridine isomer (entry **47**).



Scheme 4. Scope of the reaction using imine **22** as substrate.

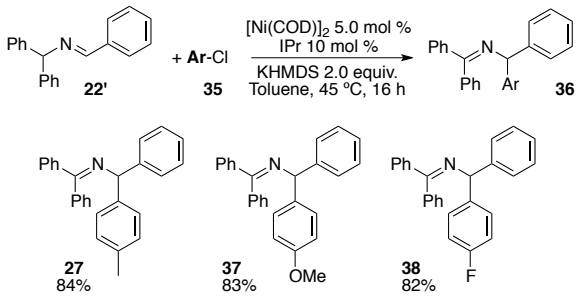
The use of other imine substrates was also explored (**Scheme 5**). Imines bearing a 4-methyl, 4-methoxy and a 4-fluoro substituent on the phenyl ring of the benzylamine building block reacted productively with chlorobenzene, generating the desired products in 86% and 82% yield respectively, enabling the synthesis of compounds **37** and **38** from a different route. On the converse, heterocyclic cores were not tolerated on the benzylamine moiety, as proven by the lack of production of compounds **52** and **53** under the reaction conditions.



Scheme 5. Scope of the reaction using different benzylic imine derivatives as substrates.

The commercially available imine **22'** was next tested. The deprotonation of this substrate, converges to the same intermediate **23**, generated by the isomer substrate **22** (as shown in **Section 5.1**, **Scheme 3**), leading therefore to the same general product after the reductive elimination. Exposure of substrate **22'** to the optimised reaction

conditions led to formation of the desired coupling products in good yield regardless of the electronic features of the chloroarene: 4-chlorotoluene, 4-chloroanisole and 4-fluoro-chlorobenzene afforded 82%-84% isolated yield of the arylated products **27**, **37** and **38** (see **Scheme 6**).

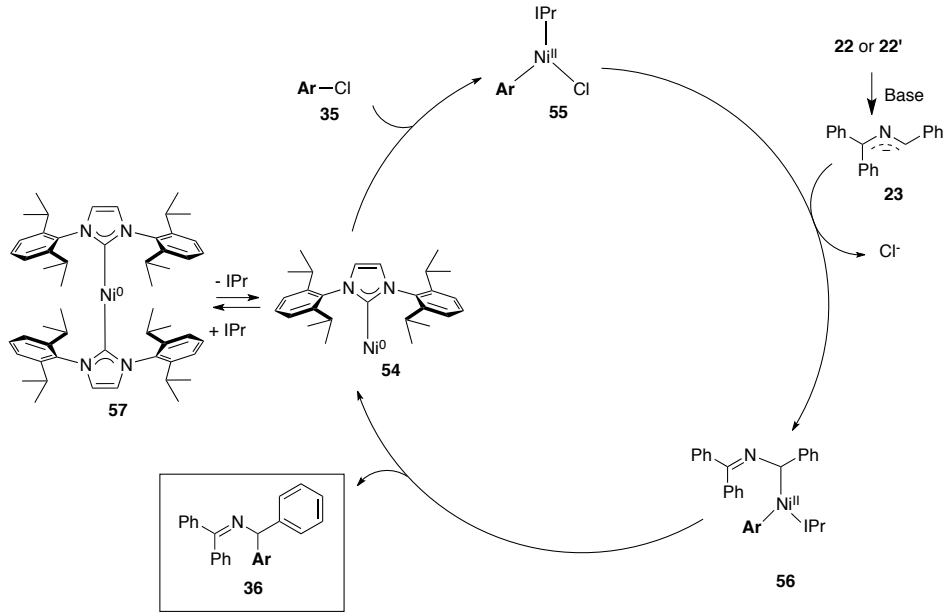


Scheme 6. Scope of the reaction using imine **22'** as substrate.

5.4 The role of the base and the putative mechanism

A reaction mechanism can be proposed based on our findings (see **Scheme 7**): the cycle is started when the catalytically active Ni^0 **54** species activates the C–Cl bond of the electrophile, forming the Ni^{II} complex **55**; this complex undergoes a transmetalation step with the aza-allyl anion **23**, generated by deprotonation of imine **22** or **22'**. The species **56** formed this way undergoes a reductive elimination step, forming the desired C–C bond and the catalytic species **54**. Such a schematic mechanism, however, does not explain the effect of the excess ligand, an interesting (and somehow surprising) feature of this protocol. As showed in the optimisation table, increasing the equivalents of IPr from 1.2 to 2.0 with respect of Ni, a small improvement in the NMR yield of the desired product, from 85% to 93% (see **Table 2**, entries **10** and **12**) was observed. When the amount of ligand was further increased to 3.0 equivalents, however, the reaction was completely shut down and led to no desired product at all (**Table 2**, entry **13**). This observation can be rationalised by postulating that a monoligated species is involved in the rate-limiting step of the reaction, whereas a bis-ligated species **57** acts as an off-cycle species. A deleterious effect of excess of NHC ligand was previously observed in the Buchwald-Hartwig reaction by Yang;[12] interestingly, the preferred L/Ni ratio in this case was 1 and not 2, using the same ligand (IPr). Two hypothesis can be proposed: 1) the bis-ligated species is formed by coordination of one IPr ligand to the unstable [Ni^0(IPr)]catalytic species **54**, preventing its decomposition by means of steric shielding and increased electronic saturation; 2)

the second IPr ligand coordinates the Ni^{II} species **55**, generating a complex of formula $[Ni(L)_2X^1X^2]$, which would be thermally and chemically stable. The coordination of an additional NHC to species **56**, bearing already the very bulky aza-allyl moiety, is less likely for steric reasons, although it cannot be excluded at this stage of development of the reaction. In both cases, the increased concentration of IPr in the reaction medium would lead to a shift of the equilibrium towards an off-cycle, inactive bis-ligated species, causing the dramatic drop in conversion.

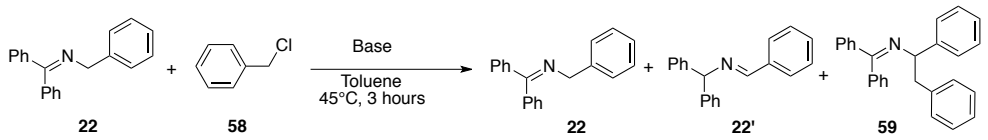


Scheme 7. Proposed mechanism for the benzylic arylation of imines.

The peculiar effect of the nature of the base in this reaction prompted us to further study the deprotonation step, clarifying the role of this additive. We first performed the alkylation of substrate **22** under the reaction conditions (toluene, 45 °C) in the absence of the catalyst (see **Table 3**). Three different bases were employed: KO*t*Bu, NaHMDS and the optimal KHMDS. The use of a base weaker than the azaallyl anion (pk_a = 24.7), such as a *t*-butoxide (pk_a = 29.4),[13] generated lower amounts of benzylated product (entry **3**); NMR analysis revealed the presence of significant amounts of side-products, that were completely absent in the reactions using HMDS containing-bases (entries **1** and **2**). The observation that both the HMDS bases led to improved results, with no clear effect of the cation, led us to test NaHMDS and KHMDS in the absence of the benzyl chloride electrophile: while the latter leads only to the formation the expected starting material (together with the isomeric compound **22'**, entry **4**), the use

of NaHMDS resulted in the formation of other products, as showed by the NMR analysis (entry **5**). Finally, KHMDS was tested in the presence of the [Ni(COD)$_2$]/IPr catalytic system, and also in this case only starting material **22** and the isomerised imine **22'** were detected. The subtle effect of the base on the overall reaction outcome is therefore explained by the generation of side products when using a non-optimal base. The contribution of the anionic part of the base is clearly related to its relative strength and nucleophilicity: the strong, non-nucleophilic HMDS performs much better than *t*-butoxides, which on the convert lead to the formation of by-products. The effect of the cation, instead, could be attributed to its hard-soft properties (as already demonstrated for other deprotonative couplings, namely the α-arylation of ketones).

Table 3. Study of the role of the base.



Entry	Base (equiv.)	**58** (equiv.)	**22**[a]	**22'**[a]	**59**[a]	Notes
1	KHMDS (2.0)	2.0	-	-	81	-
2	NaHMDS (2.0)	2.0	-	-	80	-
3	KO*t*Bu (2.0)	2.0	-	-	60	Side products observed
4	KHMDS (0.5)	-	74	26		Only **22** and **22'** observed
5	NaHMDS (0.5)	-	74	26		Side products observed
6[b]	KHMDS (0.5)	-	74	26		Only **22** and **22'** observed

Conditions: 22 (0.2 mmol, 1.0 equiv), **58** (none to 0.24 mmol, 1.2 equiv), base (0.4 mmol or 0.1 , 2.0 or 0.5 equiv.), toluene (0.6 mL), 45 °C, 3h. a) Conversion calculated by NMR analysis; b) reaction performed in the presence of 5.0 mol% [Ni(COD)$_2$], 10 mol% IPr.

The systematic rationalisation of the role and the effect of the base is a very important challenge in CC chemistry, and it is still far from being accomplished. For the purpose of our work, we can only take note of the fact that closely related bases have significantly different effects on the reaction.

5.5 Conclusions and outcome

The first Ni-catalysed deprotonative CC involving benzylic C–H bond was disclosed. The protocol involves the use of a catalyst prepared *in situ* using IPr as the optimal ligand, which outperformed the well-defined pre-catalysts that are often the most efficient tool to achieve such reactivity. The method shows a satisfyingly wide scope, including biologically important functional groups, and it is user-friendly, as it does not involve slow addition of the base and is based on a commercially available catalytic system. The role of the base proved crucial, and the ability of KHMDS to cleanly provide the nucleophilic coupling partner, the aza-allyl anion, is the basis of its superior performances. The optimisation shows that the metal/ligand ratio has a paramount effect on the reaction outcome, although deeper mechanistic studies are necessary to understand the exact reaction pathway. This project shows the possibility to expand the use of Ni catalysis to a CC reaction that is both challenging and highly valuable. Further developments of Ni catalysis are foreseeable, as this metal is proving to be a valuable alternative to Pd for many applications.

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6 Aqueous Pd-catalysed α-arylation of ketones

6.1 Aqueous cross couplings: from methodology development to functionalisation of biomolecules

The development of synthetic methods that are tolerant towards complex and highly functionalised substrates, allowing the modification of challenging biological (macro)molecules and natural products, has received ever-increasing attention over the last decades.[1] To this aim, Pd-catalyzed CCs represent an irreplaceable toolbox, as they provide synthetic access to numerous scaffolds of great interest. The effort towards milder and more efficient protocols has resulted in the development of improved methodologies, requiring lower temperatures and milder additives. Such methodologies display wider functional group tolerance, and allow the modification of remarkably complex and highly functionalised molecules.[2] Many catalytic systems have been designed for performing aqueous CC chemistry. Examples of water-soluble ligands, allowing such class of reactions to occur, are shown in **Figure 1**.

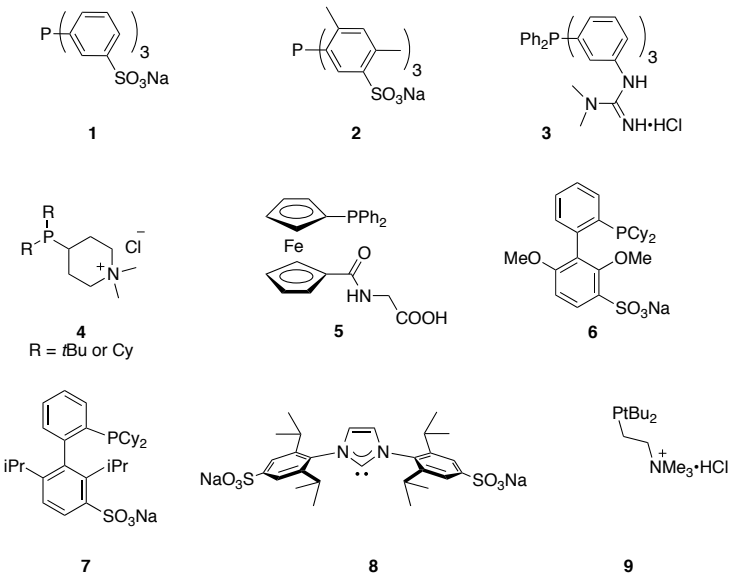
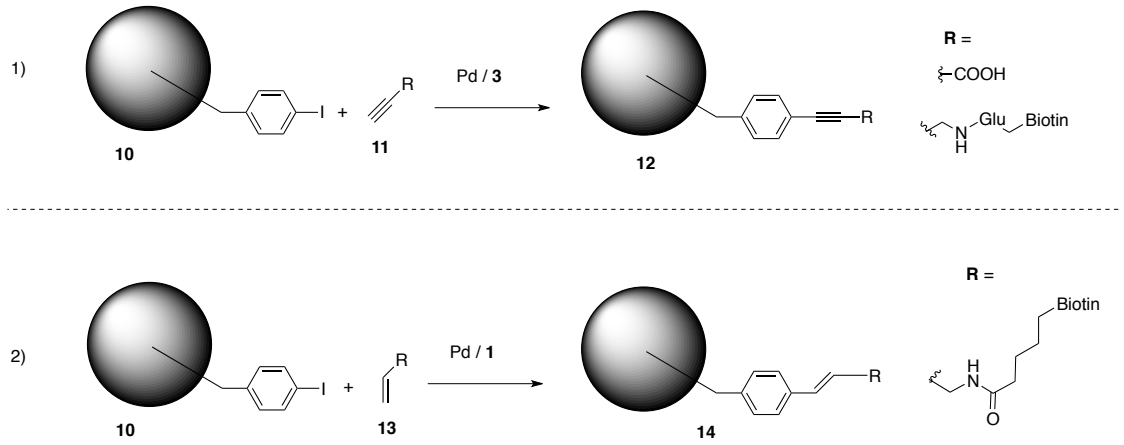


Figure 1. Water-soluble ligands for aqueous CC chemistry.

PPh_3-derived compounds, whose solubility in water is improved by anionic (sulphonate, entries **1** and **2**) or cationic (guanidium, entry **3**) substituents on the aromatic rings, are commonly used for aqueous CC.[3] Other, more complex ligands, namely specifically designed phosphines (for example ^{s}Sphos **6** and ^{s}XPhos **7**) and

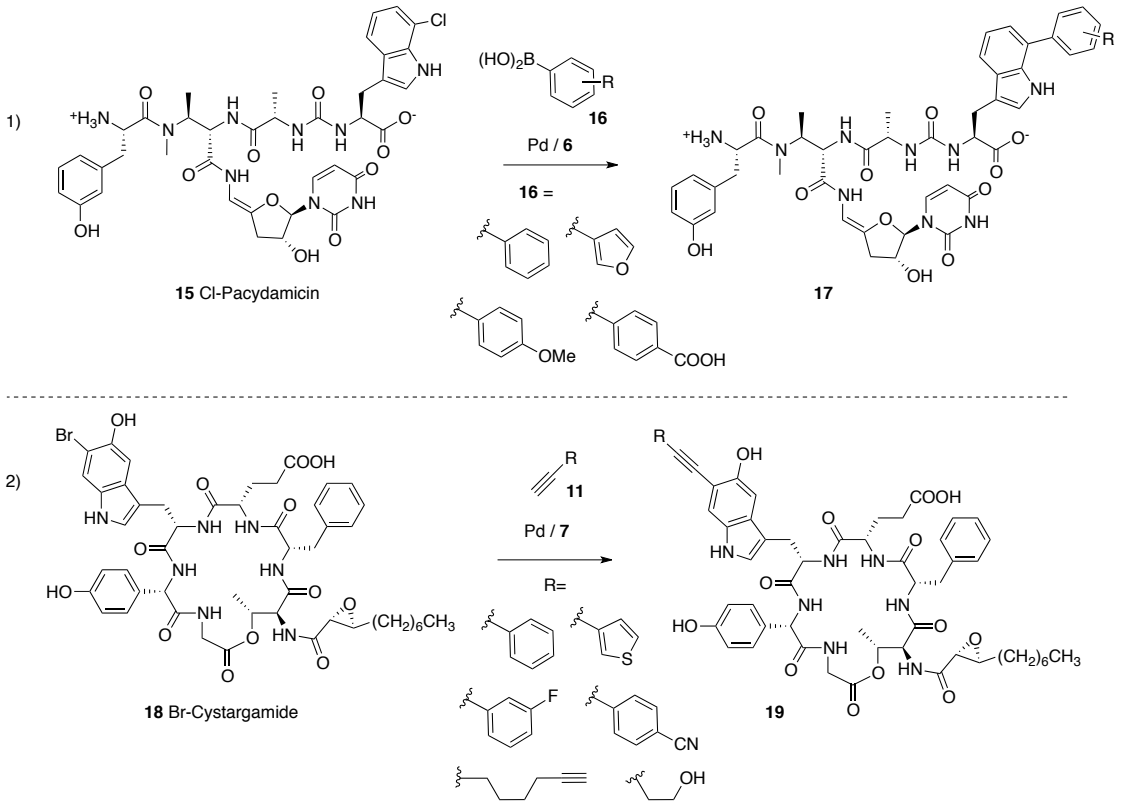
NHCs (entry **8**), are also known. Trialkylphosphines bearing a cationic ammonium moiety (entries **4** and **9**) and ferrocenyl derivatives, harnessed with an amino acid moiety, are reported, too (entry **5**).[4]

The derivatisation of complex biomolecules is often a challenging task, as the rich substitution patterns of proteins, (pseudo)peptides and most natural products hampers the reactivity by poisoning the Pd-phosphine catalyst through chelation, or leading to side-reactions. However, cases of functionalization of biomolecules using phosphines as ligands are known. One important early example was reported by Schmidtchen in 1998, using the guanidine-containing phosphine **3** to enable the Sonogashira coupling on iodophenylalanine-containing peptides (see Eq. 1 in **Scheme 1**),[5] while Fukuzawa disclosed the use of the anionic TPPTS phosphine **1** in the Heck reaction on proteins (Eq. 2 in **Scheme 1**).[6]



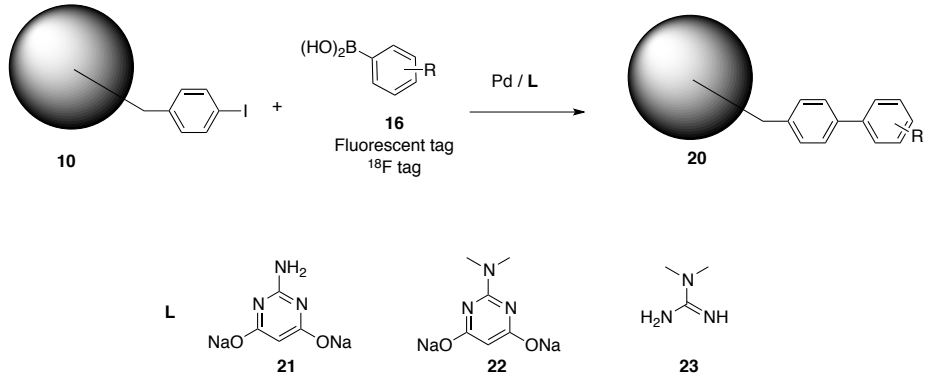
Scheme 1. Examples of Sonogashira (equation 1) and Mizoroki-Heck (equation 2) on biomolecules, according to Schmidtchen and Fukuzawa respectively.[5,6]

Goss reported the use of ^{s}SPhos **6** and ^{s}XPhos **7**, respectively, for the derivatisation of the halogenated analogues of the peptidic natural products Pacidamycin and Cystargamide. These protocols show the great flexibility of CC chemistry (Suzuki-Miyaura and Sonogashira coupling), even in the case of heavily functionalised substrates (see equation 1 and 2, respectively, in **Scheme 2**).[7]



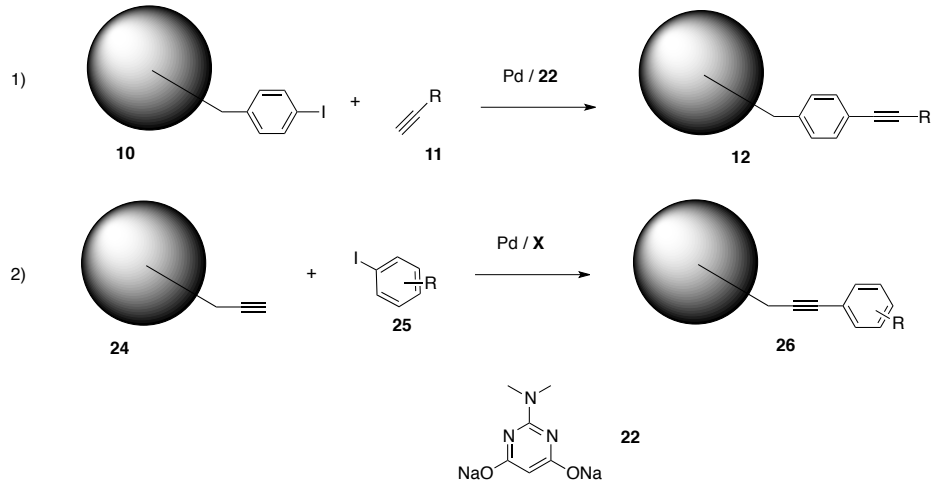
Scheme 2. Aqueous Suzuki-Miyaura (equation 1) and Sonogashira (equation 2) on natural products, according to Goss.[7]

More recently, the issue of coupling biomolecules in aqueous conditions has been addressed by the employment of the class of nitrogen-based ligands reported by Davis, who employed the simple guanidine derivatives **21-23** previously disclosed by Li for the Sonogashira coupling.[8] These simple, inexpensive compounds proved extremely active for the aqueous Suzuki-Miyaura CC of halogen-containing biomolecules (see **Scheme 3**).[9] Davis subsequently reported the use of this class of ligands for the modification of proteins, including cell surface labeling[10] and ^{19}F-tagging.[11]



Scheme 3. Coupling of biomolecules according to Davis, using the guanidine-derived ligands **21-23**.[9-11]

Ligand **22** was reported to promote the Sonogashira coupling on proteins by two different groups: Wombacher proved its utility when a halogen-containing protein derivative was reacted with an alkyne endowed with a fluorescein moiety (equation 1 in **Scheme 4**),[12] whereas Li employed an alkyne-containing protein, labelling it with a fluorogenic iodoarene (equation 2 in **Scheme 4**).[13] Notably, all the examples summarised in Scheme 3-4 required the presence of an iodo-derivative, whereas examples of chloro- and bromo-arene derivatives as substrates for peptide functionalization remain scarce, given their lower reactivity with most catalytic systems.



Scheme 4. Sonogashira coupling on proteins according to Li (equation 1) and Wombacher (equation 2).[12,13]

Aqueous CC protocols are not widespread for all the CC-like reactions known: for example, only few examples of aqueous Buchwald-Hartwig amination protocols are known, working under Pd-phosphine catalysis (some examples are reported in **Figure 2**).[14] No applications of such protocols on proteins or other types of bio-macromolecule are reported so far.

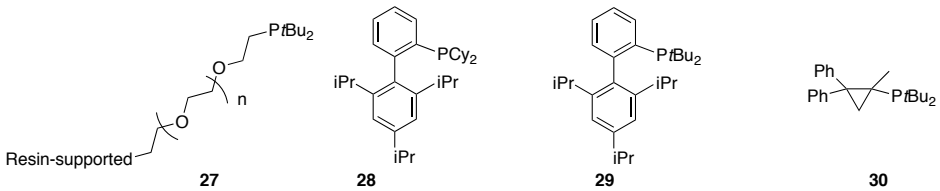
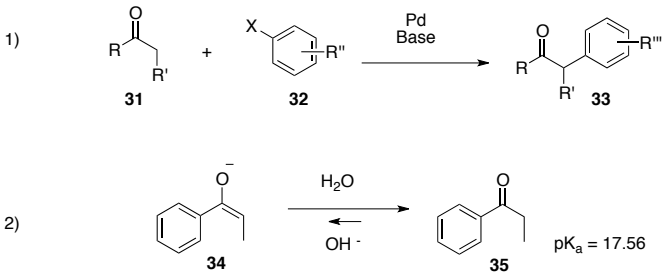


Figure 2. Examples of phosphine ligands for the aqueous Buchwald-Hartwig amination.

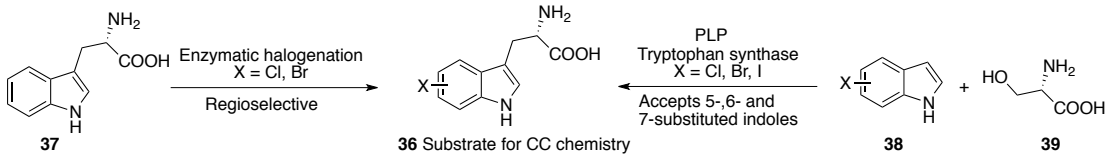
For α-arylation of ketones (whose chemical equation is reported in **Scheme 5**, equation 1), no aqueous protocols are known. The development of such an aqueous version would need to overcome the challenges arising from the use of enolates, generated by

in situ deprotonation of the ketone pro-nucleophiles. The α-proton of organic carbonyl compounds is, indeed, significantly less acidic than water (pK_a = 14);[15] therefore its conjugated base (the enolate) would be present in small concentrations at the equilibrium when water is present (see **Scheme 5**). Although the complete deprotonation of the ketone is generally not necessary for this CC to happen, the presence of a vast amount of a relatively acidic compound as solvent surely represents a challenge. The well-known use of surrogates (namely, silyl-enolethers) would lead to formation of the enolate under milder conditions,[16] but the equilibrium mentioned above would still be problematic.



Scheme 5. The equation α-arylation of ketones (equation 1) and the enolate-ketone equilibrium (equation 2).

The development of a deprotonative aqueous methodology would represent an important step in the field, as it will make the α-arylation of ketones more environmentally sustainable, while widening its potential applicability. In particular, our aim was to develop a protocol allowing the coupling of halogenated tryptophan derivatives. S-tryptophan is a natural, proteinogenic amino acid, often found to have a role in the secondary and tertiary structure of proteins; it is also a widespread moiety found in natural products. As it contains an indole moiety in the side chain, tryptophan is also often responsible for the fluorescence properties of such compounds.[17] The synthesis of enantiopure, halogenated analogues of this compound has been achieved by our group in two ways, both involving biosynthetic transformation: 1) using tryptophan synthase, an enzyme that generates S-tryptophan through coupling of a substituted indole and serine, in the presence of PLP cofactor;[18] 2) *via* enzymatic halogenation *in vivo*.[19]

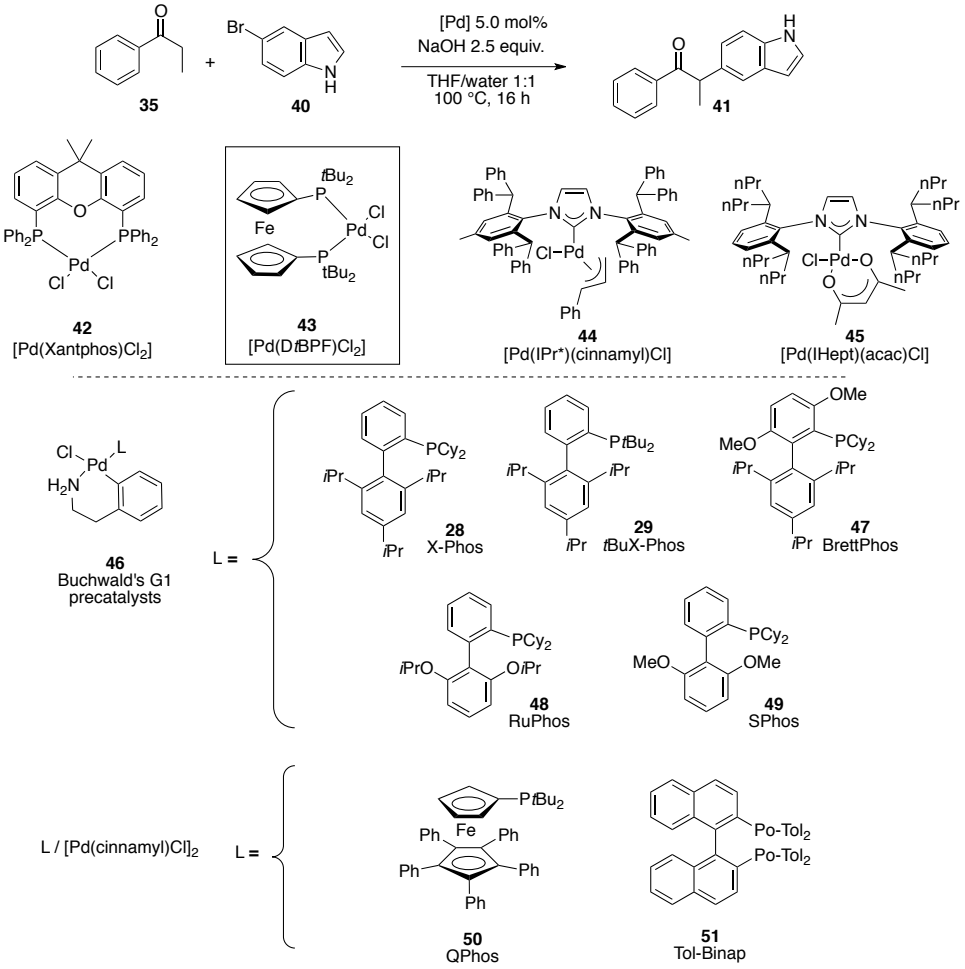


Scheme 6. Biosynthetic pathways towards halotryptophans **36**.[18,19]

The insertion of an orthogonal chemical handle (the halogen atom) to the amino acid opens the possibility for subsequent derivatisation of the compound itself, or of its (bio)synthetic derivatives. The halogenation/CC approach potentially allows the late-stage functionalisation of such compounds, and would represent a powerful tool for molecular diversification.

6.2 Identification of the pre-catalyst, optimisation, and troubleshooting

The first step of our studies involved the identification of suitable conditions for α-arylation of ketones in mixed aqueous media. First, a number of precatalysts, with varying ancillary ligands, were tested in the test reaction between propiophenone **35** and 5-bromoindole **40**. While propiophenone represents a common model compound for this CC, heterocyclic compounds like haloindoles are notoriously more difficult coupling partners. We chose 5-bromoindole because our aim was to develop a protocol suitable for a wide range of heterocyclic and functionalized coupling partners, including the halogenated tryptophan derivatives biosynthesized in our lab.



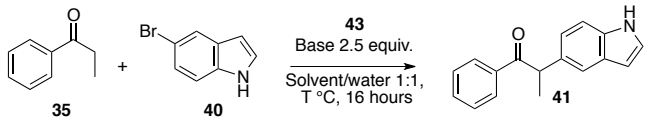
Scheme 7. Catalytic systems tested for the aqueous α-arylation. Conditions: **35** (0.4 mmol, 2.0 equiv.), **40** (0.2 mmol, 1.0 equiv.), NaOH (0.5 mmol, 2.5 equiv), catalyst (5.0 mol %), 0.5 M in THF/water 1:1 mixture , 100 °C, 16h. Conversion measured by GC analysis.

Of all the pre-catalysts tested, only complex **43**, [Pd(D*t*BPF)Cl$_2$], was found to be active in water/solvent mixtures, while other phosphine- and NHC-based catalysts were unable to perform the reaction (see **Scheme 7**). Complex **42** is known to catalyse the α-arylation of ketones in presence of traces of water, and its activity under mixed aqueous conditions is therefore not surprising. To note, the pre-treatment of the solvent through basic alumina was required to guarantee the reproducibility of the reaction outcome, as already observed by Colacot.[20]

Once the precatalyst was identified, we proceeded to screen the base/solvent system, which plays a crucial role in this cross coupling (as shown in previous Chapters). We found that, of the five water-miscible solvents tested, three provided quantitative GC conversion using NaOH as base (THF, Dioxane and *t*-amyl alcohol, entries **1**-**3** in **Table 1**). On the contrary, ethanol (entry **4**) gave no conversion to the desired product,

affording the de-halogenation product indole instead.[21] DMF (entry **5**) gave conversion lower than 10%, with traces of de-halogenation as well. The selection of the best base/solvent system was then performed by lowering both temperature and catalyst loading, screening LiOH, NaOH and KOH in the three successful solvents (entries **6-15**). NaOH in dioxane was found to be the optimal system for the reaction, affording full conversion (entry **14**), whereas other bases proved less efficient: the second-highest conversion observed was 77% using KOH in dioxane (entry **10**). The reaction summarized in entry **14** was monitored by quantitative ^{1}H NMR, using (1,3,5-tris-*t*-butyl)-benzene as internal standard, to verify the yield obtained. Surprisingly, the NMR yield of this reaction was remarkably low (65%). Increasing the catalyst loading to 5 mol% and/or the temperature to 80°C, did not significantly improve the perfomances, leading to NMR yields as high as 70% at best (entries **16-18**). The use of weaker bases, namely K_3PO_4 and Na_2CO_3, gave even lower yield (22% and 41% respectively, entries **19-20**). The NMR spectrum showed absence of 5-bromoindole in the reaction crude after a simple filtration on magnesium sulfate.

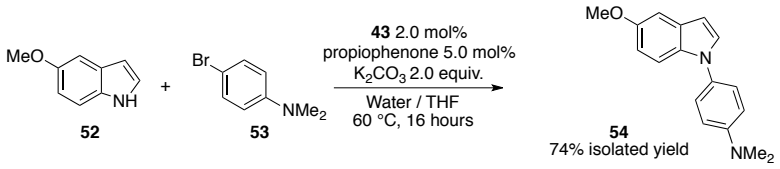
Table 1. Optimisation of the base/solvent system.



Entry	Pd loading (mol %)	Base	Solvent	T °C	Conversion%[a] (Yield %[b])
1	5	NaOH	THF	100	>99
2	5	NaOH	Dioxane	100	>99
3	5	NaOH	*t*AmOH	100	>99
4	5	NaOH	EtOH	100	n.r. [c]
5	5	NaOH	DMF	100	<10 [c]
6	2	LiOH	THF	60	51
7	2	LiOH	Dioxane	60	67
8	2	LiOH	*t*AmOH	60	41
9	2	KOH	THF	60	65
10	2	KOH	Dioxane	60	77
11	2	KOH	*t*AmOH	60	48
12	2	LiOH	Dioxane	60	67
13	2	NaOH	THF	60	57
14	2	NaOH	Diox	60	>99 (65)
15	2	NaOH	*t*AmOH	60	67
16	2	NaOH	Dioxane	80	>99 (70)
17	5	NaOH	Dioxane	60	>99 (66)
18	5	NaOH	Dioxane	80	>99 (70)
19	2	K_3PO_4	Dioxane	60	>99 (22)
20	2	Na_2CO_3	Dioxane	60	>99 (41)
21[d]	2	NaOH	Dioxane	60	>99 (90)

Reaction conditions: 35 (0.4 mmol, 2.0 equiv), **40** (0.2 mmol, 1 equiv), base (0.5 mmol, 2.5 equiv), [Pd(DtBPF)Cl_2] 2–5 mol %, 0.5 M in solvent/water 1:1 mixture , 60 or 80 °C, 16h. [a] Conversion of **40** was measured by GC analysis. [b] Yield was determined by quantitative ^{1}H NMR spectroscopy by using 1,3,5-tri-t-butylbenzene as internal standard. [c] dehalogenation product (indole) was detected at the GC; [d] Propiophenone (4.0 equiv) and NaOH (4.0 equiv) were used; 84% isolated yield.

We hypothesized that a parasitic side reaction, involving coupling between the N–H bond and the C–Br bond of 5-bromoindole, producing insoluble oligomers, was responsible for the low yields observed. Such a behavior was confirmed by the control reaction between 5-methoxyindole **52** and 4-(dimethylamino)-bromobenzene **53**, which lead to 74% isolated yield of the N-arylated product **54** under the reaction conditions used for the α-arylation of ketones.



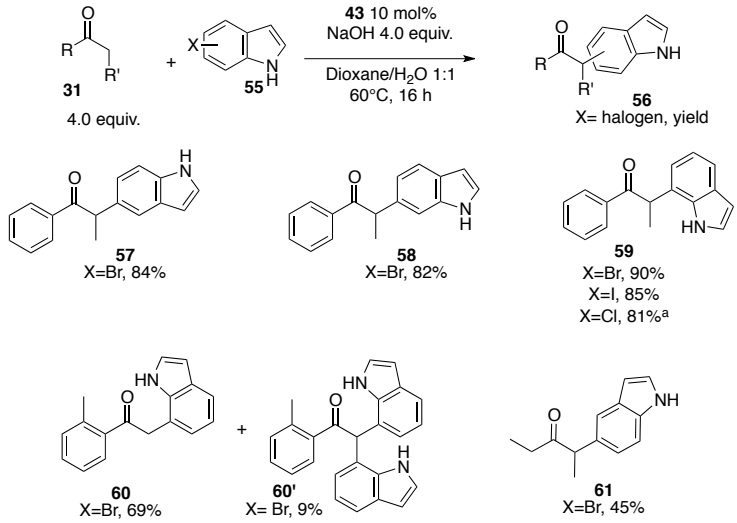
Scheme 8. Parasitic, Pd-catalysed N–H arylation under the reaction conditions.

To overcome this drawback, we decided to increase the amount of both propiophenone and base to 4 equivalents each, and therefore forcing the desired coupling by mass action (according to Le Chatelier's principle). The approach proved successful, as the NMR yield was increased to 90%, leading to an isolated yield of 84% after column chromatography (entry **21** in **Table 1**). This relatively large excess of propiophenone is doubtlessly a drawback of this method. However, we expected it to not be needed in cases where the competitive N-arylation is not possible (for example, when a N–H bond is not present, *vide infra*). The reaction temperature and catalyst loading are comparable to previous reports.

6.3 Scope of the reaction using "conventional" haloarenes

Once the optimal conditions for the reaction were found, we started exploring its scope (see **Scheme 9**). At first, we investigated the suitability of our protocol in the coupling of various haloindoles: 5-, 6- and 7-bromoindole were all successfully coupled with propiophenone in high yields (84%, 82% and 90% isolated yield respectively, entries **57-59**). To verify the effect of the halogen, compound **59** was synthesized employing 7-chloro-and 7-iodoindole: while the latter gave only a slightly lower yield compared to its brominated congener (85%), the former required an increased catalyst loading to restore full conversion and a synthetically useful yield (from 2 to 5 mol%, 81% yield). Different ketones were screened: the use *o*-methylacetophenone resulted in modest yield of the monoarylated compound **60** when 7-Bromoindole was used (69%), with the contemporary formation of the diarylated congener **60'** (9%). The lack of selectivity

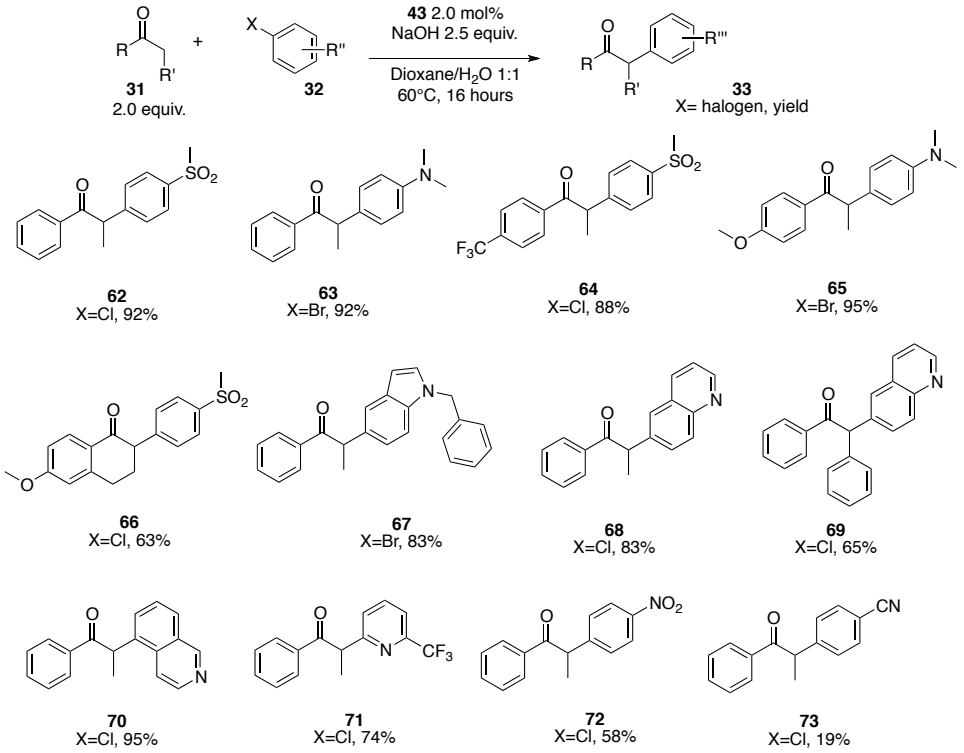
of pre-catalyst **43** when acetophenone derivatives are used is well known in the literature,[22] and this result confirms this feature, independently from the base/solvent system chosen.



Scheme 9. Scope of the reaction using haloindole derivatives.

The extension of the reaction to other functionalised haloarenes was then investigated: medicinally relevant functional groups, such as sulphones and tertiary amines, were compatible (both 92% isolated yield, entries **62** and **63**). Both electron-rich and electron-poor propiophenone derivatives were tolerated, and afforded high to very high yields (88% and 95% yield, entries **64** and **65**), while cyclic derivatives proved less efficient under the same conditions, as a significantly lower yield was obtained (63% yield, entry **66**). The effect of N-protection of 5-bromoindole was also studied: functionalization of the N-benzylated derivative was possible (83% yield, entry **67**). Notably, lower amounts of ketone and base were required, compared to haloindoles, in all of these cases (2.0 and 2.5 equiv. respectively), confirming the presence of a side reaction involving the unprotected N–H bond.

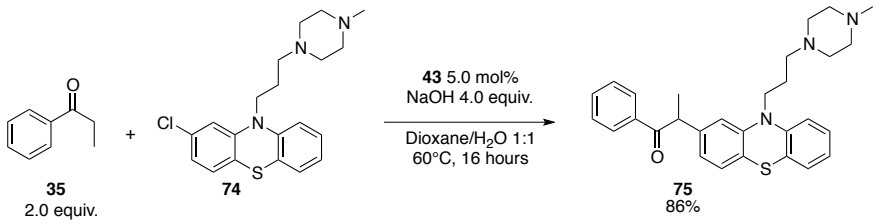
Other heterocyclic cores, namely quinolines, isoquinolines and pyridines, could also be coupled with propiophenone in good yield (83%, 95% and 74% yield respectively, entries **68, 70** and **71**). Deoxybenzoin (phenyl-benzyl-ketone) provided fair yield of the coupled product with 6-chloroquinoline (65% yield, entry **69**). Functional groups that are not well-tolerated by the excess of strong bases usually employed in this reaction,[23] such as the nitro and the nitrile moiety, were successfully coupled, although only in low to moderate yields (58% and 19% isolated yield respectively, entries **72** and **73**).



Scheme 10. Scope of the reaction using other haloarenes.

6.4 Coupling of Prochlorperazine and halotryptophans.

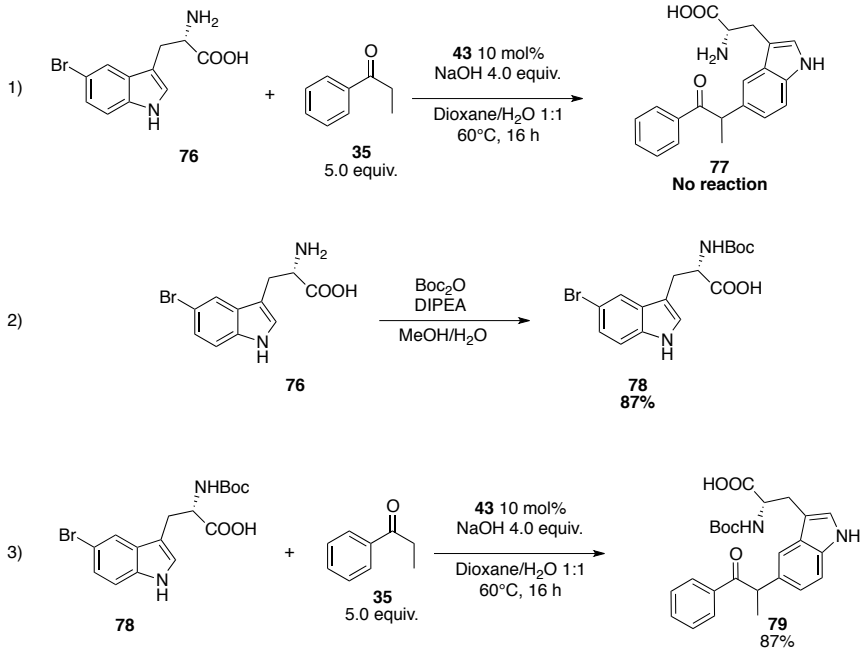
To test the applicability of this methodology to "real-world" bioactive molecules, the halogenated over-the-counter drug Prochlorperazine **74** was chosen as a more complex model substrate. **74** was developed as an antipsychotic drug and antiemetic, and recent research has proven its antimicrobial activity.[24] The reaction protocol was then followed using 5.0 mol% catalyst loading and 4 equivalents of base, affording 86% isolated yield of the product **75**.



Scheme 11. Coupling of Prochlorperazine.

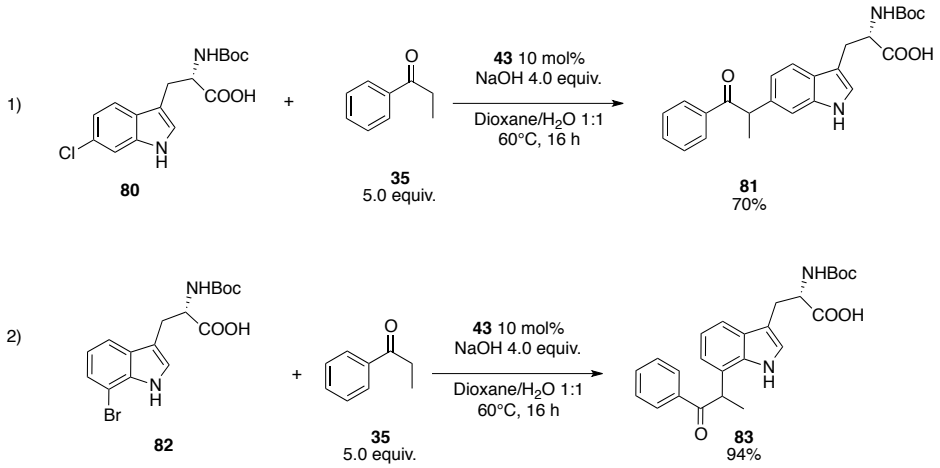
Once the scope of the reaction was addressed with "conventional" coupling partners and small-molecule drugs, the stage was set for the extension of the protocol to halogenated tryptophan derivatives. Attempts to perform the reaction on fully unprotected 5-Bromotryptophan **76** afforded no conversion to the desired product, even when the reaction was performed under more forcing conditions (see equation 1

in **Scheme 12**). Hence, the amine group of compound **76** was protected, affording the desired *S*-(N-Boc)-5-bromotryptophan **78** in 87% yield (see equation 2 in **Scheme 12**). Pleasantly, **78** was found to react under the developed conditions, affording 87% yield of the desired coupled product **77** (see equation 3 in **Scheme 12**).



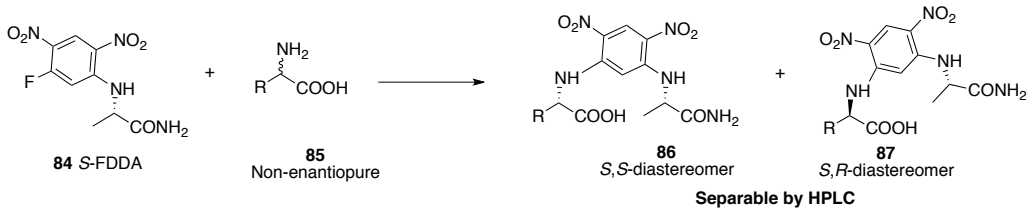
Scheme 12. Attempted coupling of unprotected *S*-5-Bromotryptophan **76** (equation 1); Boc-protection of **76** affording *S*-(N-Boc)-5-bromotryptophan **78** (equation 2); coupling of **78**.

The amine group of *S*-6-chlorotryptophan and *S*-7-bromotryptophan were also Boc-protected (affording 88% and 91% yield, respectively), and the N-capped amino acids **80** and **82** were subsequently coupled with propiophenone. The coupling was successful, affording 70% and 94% yield, respectively (entries **81** and **83** in **Scheme 13**).



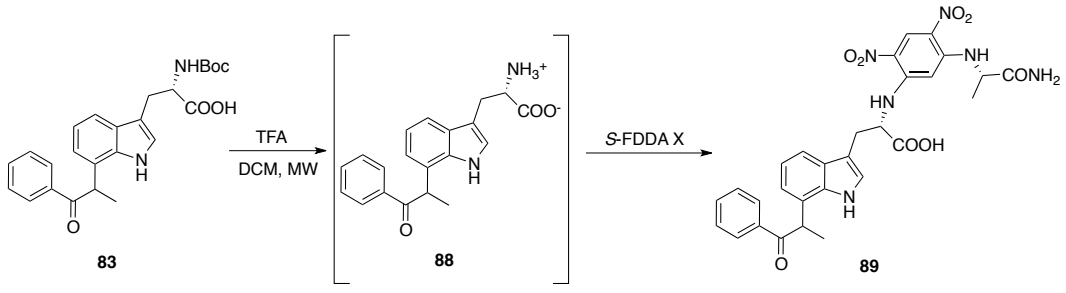
Scheme 13. Coupling of *S*-(N-Boc)-6-chlorotryptophan **78** (equation 1) and of *S*-(N-Boc)-7-bromotryptophan (equation 2).

The compatibility of the reaction conditions (especially the excess of base) with enantiomerically pure amino acids was a critical point of concern. Racemisation of the stereocenter of the biosynthesised, enantiopure amino acid could lead to undesired mixtures of enantiomers, which would represent a significant drawback for applications on biomolecules. To verify the tolerance of our protocol towards the stereocenter of the amino acid, Marfey's test was performed. This analytical method entails the coupling of an amino acid with Marfey's reagent, N-(2,4-dinitro-5-fluorophenyl)-*S*-alaninamide (FDDA) **84**. The two diastereomers that arise when a non-enantipure amino acid is employed are separable by HPLC analysis (see **Scheme 14**). As such, Marfey's test provides a semi-quantitative assessment of the enantiomeric purity of an amino acid derivative.[25]



Scheme 14. General equation for Marfey's test of enantiopurity.

As Marfey's reagent requires an N-free amino acid substrate, we devised a stepwise sequence: product **83** was first deprotected using trifluoroacetic acid (TFA) in DCM, under microwave irradiation. The crude solid obtained was directly coupled with *S*-FDDA, according to the protocol developed by Marfey. The resulting compound was dissolved, centrifuged and diluted to the required concentration for HPLC, comparing its analysis with standard substrates treated in parallel under the same conditions.



Scheme 15. Marfey's test on compound **83**. For experimental detail see **Chapter 7.6**.

Figure **3** contains the HPLC tracks of the following, Marfey-derivatised compounds: a) *S*-tryptophan b) *S*+*R*-tryptophan c) *S*-7-bromotryptophan and d) compound **89**. The analysis shows no detectable racemisation occurring during the coupling process,

demonstrating the suitability of our protocol for protected, enantiopure amino acid derivatives. Interestingly, the additional racemic stereocenter generated at the α-position of propiophenone during the reaction had no effect on the Marfey's test, probably because of its relatively great distance from the two stereocenters of the peptide.

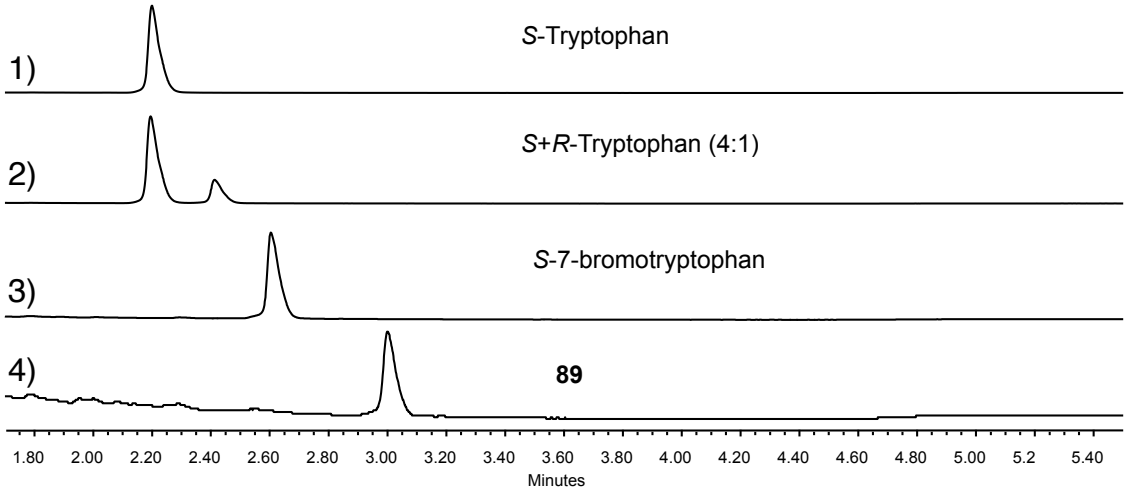


Figure 3. HPLC tracks of Marfey's analysis of *S*-Tryptophan (1), non-enantiopure tryptophan (2), S-7-bromotryptophan (3), and compound **89**, (4).

The coupling of amino acids is unprecedented in the α-arylation of ketones under Pd catalysis,[26] and represent a significant step towards the application of this DCC to biomolecules and natural products.

6.5 Conclusions and outcome

The extension of the α-arylation of ketones to aqueous media has been successfully achieved. The reaction conditions required are comparable to the related reports using the same catalyst in non-aqueous solvents, and allow the coupling of a wide range of reaction partners. As this method allows the coupling of halogenated amino acids and small-molecule bioactive molecules, it represents a significant advance both in the field of deprotonative couplings as well as in the broader context of late-stage functionalization of biomolecules and natural products. The future work will focus on the application of this method on peptides, proteins and natural products.

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7 Experimental Section

7.1 General Remarks

Anhydrous, oxygen-free dioxane, DME, DMF and isopropanol were purchased from Sigma-Aldrich, stored in glovebox and used as received. Anhydrous, oxygen free toluene and THF were obtained from an SPR machine and stored in a glovebox. Anhydrous bases (LiO*t*Bu, NaO*t*Bu, KO*t*Bu, K_2CO_3, Na_2CO_3,K_3PO_4, LiOH, NaOH, KOH, CsOH, KHMDS, LiHMDS, NaHMDS) were purchased from Sigma-Aldrich or Alfa-Aesar, stored in a glovebox and used as received. KO*t*Am, received as a 1.7 M solution in toluene, was dried on a Schlenk line, stored in a glovebox and used as a powder. Anhydrous dioxane, DME, DMF and DMA were purchased from Sigma-Aldrich and used as received.

Non-anhydrous solvents (EtOH, *t*AmOH, DMF) and bases (Na_2CO_3,K_3PO_4, LiOH, NaOH, KOH) used for the protocol reported in **Chapter 6** were purchased from Sigma-Aldrich or Alfa-Aesar and used as received. Non-anhydrous dioxane and THF were purchased from Sigma-Aldrich or Alfa-Aesar and filtered through a pad of basic alumina before use.

All commercially available chloroarene and ketone substrates were purchased from Sigma-Aldrich, Alfa-Aesar or TCI and used as received, unless otherwise noted. [Pd(cinnamyl)Cl]$_2$ and [Pd(acac)$_2$] were purchased from Strem and used as received. [Ni(COD)$_2$] was purchased from Strem and stored at -20 °C in a glovebox. [Ni(DME)Cl$_2$] and [Ni(acac)$_2$] were purchased from Sigma-Aldrich and used as received. [Pd(D*t*BPF)Cl$_2$], [Pd(XantPhos)Cl$_2$], QPhos, Tol-BINAP, and the Buchwald Precatalyst Kit G1 were purchased from Sigma-Aldrich or Alfa-Aesar and used as received.

NHC ligands and [Pd(NHC)] precatalysts were synthesized according to previously reported procedure.[1]

Halotryptophan derivatives were synthesized according to a previously reported procedure.[2]

Flash chromatography was performed on silica gel 60 Å pore diameter and 40-63 μm particle size.

^{1}H, ^{13}C and ^{19}F Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker-400 or 500 MHz spectrometer, at ambient temperature, in $CDCl_3$ or CD_3OD. Chemical shifts (δ) are reported in ppm, relative to the solvent residual proton $CDCl_3$ (7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C) or CD_3OD (3.31 ppm for ^{1}H and 49.00 ppm for ^{13}C). For ^{19}F NMR, chemical shifts refer to an external calibration using $CFCl_3$ (δ = 0.00 ppm). Data for 1H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d =

doublet, t = triplet, br = broad signal, m = multiplet), coupling constants (J) in Hz and integration.
Gas chromatography analyses (GC) were performed on an Agilent 7890A apparatus equipped with a flame ionization detector and a (5%-Phenyl)-methylpolysiloxane column (30 m, 320 μm, film: 0.25 μm). Flow rate 1 mL/min constant flow, inlet temperature 260°C, column temperature 50°C, 20°C/min increase to 300°C (held for 1 min), total time 7.6 min.
UPLC analysis was aquired on a Waters Acquity H-Class UPLC system fitted with a Waters Acquity UPLC BEH C18 column (1.7 mm, 2.1×50 mm).
All isolated yields are average of 2 runs, except from the yields reported in **Chapter 6**, which are average of 3 runs.

7.2 Experimental details for Chapter 2

Synthesis of [Pd(IHept)(acac)Cl] 20

IHept•HCl (520 mg 0.80 mmol, 1.2 eq.) and [Pd(acac)$_2$] (192 mg, 0. 64 mmol, 1 eq.) were added in a dry Schlenk flask equipped with a stirring bar. They were purged three time with vacuum/ nitrogen cycles, and then dry 1,4-dioxane (10 ml) was added under a nitrogen atmosphere. The reaction mixture was refluxed overnight. The solvent was evaporated and the crude was dissolved in pentane. The solution was filtered through a pad of silica covered with Celite, washing with pentane. After evaporation of the solvent and drying under high vacuum, the pure desired complex was obtained as a yellow powder (432 mg, 81%).

General procedure for the α-arylation of ketones using pre-catalyst 20

Inside a glovebox, a vial containing a stir bar was charged with NaO*t*Bu (105 mg, 1.1 mmol, 2.2 equivalents), Solid ketones (0.7 mmol, 1.4 equivalents) and/or aryl chlorides (0.50 mmol, 1.0 equivalents) were added at this point and dissolved in toluene, and the vial was sealed. A stock solution of **20** [Pd(IHept)(acac)Cl] in toluene was prepared and dispensed with a syringe (e.g.: 4.3 mg in 2 mL. 0.1 mL of this solution correspond to 500 ppm catalyst loading. Total reaction volume was 1 mL). Outside of the glovebox, ketone and/or the aryl chloride were added if liquids, followed by the stock solution. Finally, the vial was stirred at 600 rpm, at T= 100 °C for 16 hours. The solution was then cooled to room temperature, some drops of water were added and the crude was filtered through silica eluting with ethyl acetate. The organic layers were dried under vaccum. Column chromatography of the crude (typically hexane/ethyl acetate 9/1) gave the desired product.

Synthesis of compound 38 in air

In a screw cap vial equipped with a stirring bar, NaO*t*Bu (105 mg, 1.1 mmol, 2.2 eq.) was weighted and dissolved in 0.9 mL of dry toluene. A stock solution of **20** was

prepared in a second vial (2.6 mg in 2 mL of dry toluene). Propiophenone (90 μL, 91 mg, 0.68 mmol, 1.36 eq.), 2-Cl-anisole (71 mg, 0.5 mmol, 1 eq.) and 0.1 mL of the stock solution (corresponding to 300 ppm) were added to the vial containing the base. The vial was then sealed and magnetically stirred at 100°C overnight. The workup reported above afforded 181 mg (75%) of the desired product.

Characterisation data

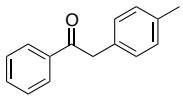
20 [Pd(IHept)(acac)Cl]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (t, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 4H), 7.02 (s, 2H), 4.98 (s, 1H), 2.82 (m, 4H), 2.17 (m, 4H), 1.77 (s, 3H), 1.40 (s, 3H), 1.73-1.25 (m, 20H), 1.15-1.08 (m, 8H), 0.80 (t, *J* = 7.1 Hz, 24H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 186.4, 184.1, 154.4, 144.8, 137.0, 129.3, 125.3, 125.6, 99.9, 40.0, 39.9, 39.1, 26.9, 26.0, 21.7, 21.2, 15.14.

Anal. Calcd for $C_{48}H_{75}ClN_2O_2Pd$: C, 67.51; H, 8.85; N, 3.28. Found: C, 67.39; H, 8.77; N, 3.39.

29. 1-Phenyl-2-(p-tolyl)ethan-1-one:[3]



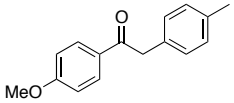
Pd loading 0.02 mol%. Yield 80%, 176 mg, yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03-8.01 (m, 2H), 7.57-7.55 (m, 1H), 7.48-7.44 (m, 2H), 7.18-7.13 (m, 4H), 4.26 (s, 2H), 2.33 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.8, 136.4, 133.1, 131.4, 129.4, 129.3, 128.6, 45.1, 21.0.

Analytical data matches previously reported characterisation.

30. 1-(4-Methoxyphenyl)-2-(p-tolyl)ethan-1-one:[3]



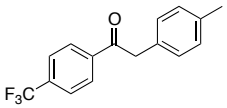
Pd loading 0.05 mol%. Yield 70%, 168 mg, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97-7.94 (m, 2H), 7.49-7.45 (m, 1H), 7.40-7.36 (m, 2H), 7.22-7.19 (m, 2H), 6.85-6.82 (m, 2H), 4.65 (q, J= 6.8Hz, 1H), 3.88 (s, 3H), 1.51 (d, J= 7.8Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.5, 158.4, 136.6, 133.4, 132.7, 128.7, 128.7, 128.4, 114.3, 55.2, 46.9, 19.5.

Analytical data matches previously reported characterisation.

31. 2-(*p*-Tolyl)-1-(4-(trifluoromethyl)phenyl)ethan-1- one:[4]



Pd loading 0.2 mol%. Yield 82%, 228 mg, pale yellow solid.

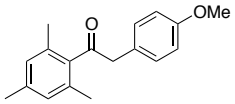
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J= 8.2 Hz, 2H), 7.71 (d, J= 8.3 Hz, 2H), 7.15 (s, 4H), 4.27 (s, 2H), 2.33 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.8, 139.2, 136.8, 134.3 (q, J_{CF}= 32.6 Hz), 130.6, 129.5, 129.2, 128.9, 125.7 (q, J_{CF}= 3.5 Hz), 123.5 (q, J_{CF}= 272.7 Hz), 45.5, 21.1.

^{19}F NMR (471 MHz, $CDCl_3$): δ -63.1

Analytical data matches previously reported characterisation.

32. 1-Mesityl-2-(4-methoxyphenyl)ethan-1-one:



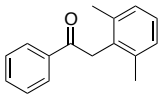
Pd loading 0.05 mol%. Yield 84%, 225 mg.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, J= 8.6 Hz, 2H), 6.87 (d, J= 8.6 Hz, 2H), 6.84 (s, 2H), 3.95 (s, 2H), 3.80 (s, 3H), 2.29 (s, 3H), 2.14 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 207.9, 158.6, 139.1, 138.4, 132.7, 130.8, 128.4, 125.2, 113.9, 55.2, 50.8, 21.0, 19.1.

HRMS: Calculated for $C_{18}H_{20}O_2$: 269.1542, Found: $[M+H]^+$ 269.1536

33. 2-(2,6-Dimethylphenyl)-1-phenylethan-1-one:[3]



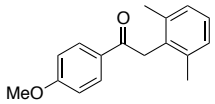
Pd loading 0.03 mol%. Yield 89%, 200 mg, colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J= 8.1 Hz, 2H), 7.62 (t, J= 7.4 Hz, 1H), 7.52 (t, J= 7.2 Hz, 2H), 7.14-7.06 (m, 3H), 4.39 (s, 2H), 2.23 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.9, 137.1, 137.0, 133.2, 132.4, 128.7, 128.1, 128.0, 126.9, 39.6, 20.4.

Analytical data matches previously reported characterisation.

34. 2-(2,6-Dimethylphenyl)-1-(4-methoxyphenyl)ethan-1-one:[3]



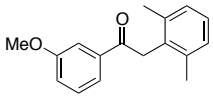
Pd loading 0.02 mol%. Yield 87%, 222 mg, white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.04 (m, 2H), 7.12-7.04 (m, 3H), 7.00-6.96 (m, 2H), 4.33 (s, 2H), 3.90 (s, 3H), 2.22 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 163.6, 137.0, 132.9, 130.4, 130.2, 128.0, 126.8, 113.9, 55.5, 39.3, 20.5.

Analytical data matches previously reported characterisation.

35. 2-(2,6-Dimethylphenyl)-1-(3-methoxyphenyl)ethanone:[5]



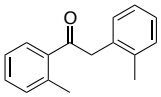
Pd loading 0.05 mol%. Yield 92%, yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J=7.6 Hz, 1H), 7.60 (br s, 1H), 7.45 (t, J=7.9 Hz, 1H), 7.17 (dd, J=8.2 Hz, J= 2.2 Hz), 7.15-7.12 (m, 1H), 7.10-7.08 (m, 2H), 4.38 (s, 2H), 3.89 (s, 3H), 2.24 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.7, 159.8, 138.4, 136.9, 132.4, 129.6, 127.9, 126.9, 120.6, 119.5, 112.4, 55.4, 21.0, 39.7, 20.3.

Analytical data matches previously reported characterisation.

36. 1,2-Di-(2-methylphenyl)ethanone:[6]



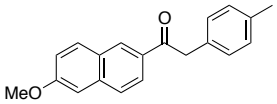
Pd loading 0.05 mol%. Yield 98%, 221 mg, colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J= 7.5 Hz, 1H), 7.39 (dt, J1= 7.5 Hz, J2 = 1Hz, 1H), 7.29-7.24 (m, 2H), 7.21-7.11 (m, 4H), 4.24 (s, 2H), 2.46 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.3, 138.3, 137.8, 136.8, 133.3, 132.0, 131.3, 130.5, 130.3, 128.4, 127.2, 126.1, 125.6, 46.4 21.2, 19.8.

Analytical data matches previously reported characterisation.

37. 1-(6-Methoxynaphthalen-2-yl)-2-(*p*-tolyl)ethan-1-one:



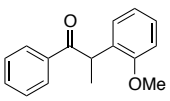
Pd loading 0.05 mol%. Yield 87%, 254 mg.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, J= 1.5 Hz, 1H), 8.04 (dd, J= 8.6 Hz, J= 1.6 Hz, 1H), 7.85 (d, J= 9.0 Hz, 1H), 7.76 (d, J= 8.7 Hz, 1H), 7.22-7.18 (m, 3H), 7.15-7.12 (m, 3H), 4.35 (s, 2H), 3.95 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 159.9, 137.4, 136.6, 132.2, 131.9, 131.3, 130.4, 129.5, 129.4, 128.0, 127.3, 125.2, 119.8, 105.9, 55.6, 45.2, 21.2.

HRMS: Calculated for $C_{20}H_{18}O_2$: 291.1385, Found: $[M+H]^+$ = 291.1382

38. 2-(2-Methoxyphenyl)-1-phenylpropan-1-one:[3]

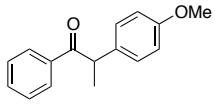


Pd loading 0.03 mol%. Yield 91%, 218 mg, yellow oil.

When performed in air, yield 75%, 179 mg.

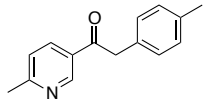
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99-7.94 (m, 2H), 7.47-7.42 (m, 1H), 7.37-7.34 (m, 2H), 7.18 (td, J= 8Hz, J= 1.7 Hz, 1H), 7.12 (dd, J= 8Hz, J= 1.6 Hz, 1H), 6.88 (d, J= 7.8Hz, 2H), 5.09 (q, J= 6.8Hz, 1H), 3.88 (s, 3H), 1.47 (d, J= 7.8Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 201.3, 155.7, 136.4, 132.5, 130.1, 128.4, 128.2, 128.0, 127.9, 120.9, 110.7, 55.4, 40.3, 17.5.
Analytical data matches previously reported characterisation.

39. 2-(4-Methoxyphenyl)-1-phenylpropan-1-one:[3]



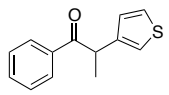
Pd loading 0.03 mol%. Yield 97%, 233 mg, yellow solid.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97-7.94 (m, 2H), 7.49-7.45 (m, 1H), 7.40-7.36 (m, 2H), 7.22-7.19 (m, 2H), 6.85-6.82 (m, 2H), 4.65 (q, J= 6.8Hz, 1H), 3.88 (s, 3H), 1.51 (d, J= 7.8Hz, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 200.5, 158.4, 136.6, 133.4, 132.7 , 128.7, 128.7, 128.4, 114.3, 55.2, 46.9, 19.5.
Analytical data matches previously reported characterisation.

40. 1-(6-Methylpyridin-3-yl)-2-(*p*-tolyl)ethan-1-one:



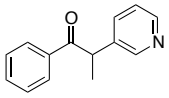
Pd loading 0.05 mol%. Yield 80%, 180 mg, brown oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (d, J= 2.0 Hz, 1H), 8.13 (dd, J= 8.1 Hz, J= 2.3 Hz, 1H), 7.22 (d, J= 8.1 Hz, 1H), 7.16-7.10 (m, 4H), 4.21 (s, 2H), 2.60 (s, 3H), 2.30 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 163.3, 149.9, 136.8, 136.3, 130.8, 129.6, 129.4, 129.3, 123.4, 45.5, 24.9, 21.1.
HRMS: Calculated for $C_{15}H_{15}NO$: 226.1231, Found: $[M+H]^+$ = 226.1225

41. 1-Phenyl-2-(thiophen-3-yl)propan-1-one:[7]



Pd loading 0.05 mol%. Yield 84%, 182 mg, brown oil.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.85 (m, 2H), 7.42-7.35 (m, 1H), 7.33-7.26 (m, 2H), 7.13 (dd, J= 4.9 Hz, J= 2.9 Hz, 1H), 6.99 -6.96 (m, 1H), 6.91 (dd, J= 5.0 Hz, J= 1.4 Hz, 1H), 4.74 (q, J= 6.9 Hz, 1H), 1.43 (d, J= 6.9 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 141.3, 136.2, 132.8, 128.6, 128.4, 127.0, 126.0, 121.3, 42.7, 18.8.
Analytical data matches previously reported characterisation.

42. 1-Phenyl-2-(pyridin-3-yl)propan-1-one:[3]



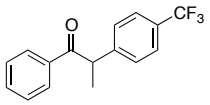
Pd loading 0.05 mol%. Yield 96%, 202 mg, brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J= 2.0 Hz, 1H), 8.46 (dd, J= 4.8 Hz, J= 1.6 Hz, 1H), 7.96-7.93 (m, 2H), 7.60 (dt, J= 7.9 Hz, J= 1.9 Hz, 1H), 7.54-7.49 (m, 1H), 7.43-7.38 (m, 2H), 4.74 (q, J= 6.9 Hz, 1H), 1.56 (d, J= 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 149.6, 148.5, 137.0, 136.0, 135.2, 133.4, 128.8, 128.8, 123.9, 45.0, 19.5.

Analytical data matches previously reported characterisation.

43. 1-Phenyl-2-(4-(trifluoromethyl)phenyl)propan-1-one:[3]



Pd loading 0.05 mol%. Yield 81%, 225 mg, brown solid.

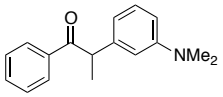
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.92 (m, 2H), 7.56 (d, J= 8.1 Hz, 1H), 7.54-7.49 (m, 1H), 7.44-7.38 (m, 4H), 4.77 (q, J= 6.9 Hz, 1H), 1.56 (d, J= 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 145.5, 136.2, 133.3, 129.2 (q, J_{CF}= 32.5 Hz), 128.9, 128.8, 128.3, 126.1 (q, J_{CF}= 3.7 Hz), 124.1 (q, J_{CF}= 271.9 Hz), 47.6, 19.6.

^{19}F NMR (377 MHz, $CDCl_3$): δ -62.5

Analytical data matches previously reported characterisation.

44. 2-(3-(Dimethylamino)phenyl)-1-phenylpropan-1-one:



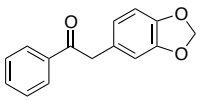
Pd loading 0.05 mol%. Yield 85%, 215 mg, green solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.95 (m, 2H), 7.48-7.43 (m, 1H), 7.39-7.34 (m, 1H), 7.16 (t, J= 7.9 Hz, 1H), 6.64 (d, J= 7.6 Hz, 1H), 6.61-6.55 (m, 2H), 4.61 (q, J= 6.8 Hz, 1H), 2.91 (s, 6H), 1.53 (d, J= 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 151.0, 142.4, 136.7, 132.6, 129.6, 128.7, 128.4, 116.1, 111.5, 111.0, 48.5, 40.5, 19.5.

HRMS: Calculated for $C_{17}H_{19}NO$: 254.1445, Found: $[M+H]^+$ = 254.1541

45. 2-(Benzo[d][1,3]dioxol-5-yl)-1-phenylethan-1-one:[4]

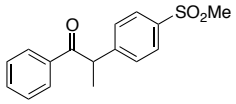


Pd loading 0.02 mol%. Yield 84%, 203 mg, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02-7.99 (m, 2H), 7.59-7.54 (m, 1H), 7.49-7.43 (m, 2H), 6.78-6.69 (m, 3H), 5.93 (s, 2H), 4.20 (s, 2H).

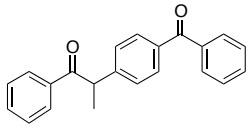
^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 148.0, 146.7, 136.7, 133.3, 128.8, 128.7, 128.2, 122.7, 110.0, 108.6, 101.1, 45.2.
Analytical data matches previously reported characterisation.

46. 2-(4-(Methylsulfonyl)phenyl)-1-phenylpropan-1-one:



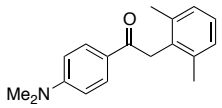
Pd loading 0.05 mol%. Yield 70%, 203 mg, white solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J= 7.4 Hz, 2H), 7.87 (d, J= 8.3 Hz, 2H), 7.55-7.48 (m, 3H), 7.41 (t, J= 7.7 Hz, 2H), 4.81 (q, J= 6.9 Hz, 1H), 3.01 (s, 3H), 1.56 (d, J= 6.9 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 147.7, 139.2, 136.0, 133.5, 129.0, 128.9, 128.8, 128.1, 47.5, 44.6, 19.5.
HRMS: Calculated for $C_{16}H_{16}O_3S$: 306.1164, Found: $[M+NH_4]^+$ = 306.1161

47. 2-(4-Benzoylphenyl)-1-phenylpropan-1-one:[8]



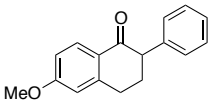
Pd loading 0.05 mol%. Yield 81%, 225 mg, yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.94 (m, 2H), 7.77-7.73 (m, 4H), 7.60-7.55 (m, 1H), 7.54-7.49 (m, 1H), 7.48-7.39 (m, 6H), 4.79 (q, J= 6.9 Hz, 1H), 1.58 (d, J= 6.9 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 196.3, 137.7, 136.4, 133.2, 132.5, 131.0, 130.1, 128.9, 128.8, 128.4, 127.9, 47.9, 19.5.
Analytical data matches previously reported characterisation.

48. 1-(4-(Dimethylamino)phenyl)-2-(2,6-dimethylphenyl)ethan-1-one:



Pd loading 0.05%. Yield 78%, 208 mg, green solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-7.99 (m, 2H), 7.12-7.04 (m, 3H), 6.72-6.68 (m, 2H), 4.30 (s, 2H), 3.08 (s, 6H), 2.24 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 153.4, 137.0, 133.4, 130.2, 127.8, 126.5, 125.1, 110.6, 40.0, 38.8, 20.4.
HRMS: Calculated for $C_{18}H_{21}NO$: 268.1701, Found: $[M+H]^+$ = 268.1695

55. 6-Methoxy-2-phenyl-3,4-dihydronaphthalen-1(2H)-one:[9]



Pd loading 0.05%. Yield 93%, 235 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J= 8.7 Hz, 1H), 7.37-7.31 (m, 2H), 7.28-7.23 (m, 1H), 7.20-7.17 (m, 3H), 3.88 (s, 3H), 3.79-3.74 (m, 1H), 3.09-2.95 (m, 2H), 2.44-2.38 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1, 163.7, 146.7, 140.2, 130.4, 128.6, 128.5, 127.0, 126.7, 113.4, 112.7, 55.6, 54.2, 31.5, 29.1.

Analytical data matches previously reported characterisation.

7.3 Experimental details for Chapter 3

Synthesis od [Pd(IPr*)(cinnamyl)Cl] 42

In a glovebox, in a 500 mL round bottom flask equipped with a magnetic stirring bar were charged IPr*·HCl (2.08 g, 2.2 mmol) and KO*t*Bu (0.28 g, 2.4 mmol) along with THF (160 mL). The reaction mixture was stirred at room temperature for 4 h and then [{Pd(cinnamyl)(m-Cl)}$_2$] (0.512 g, 1 mmol) was added as a THF (40 mL) solution. The reaction mixture was then stirred overnight at room temperature. After this time, the reaction flask was taken outside the glovebox where THF was evaporated under reduced pressure, the crude product was dissolved in CH_2Cl_2, filtered on a pad of silica covered with celite, and eluted with CH_2Cl_2. After evaporation of the solvents, the complex was precipitated from pentane, and the solid collected by filtration. After drying under high vacuum for 1 hr, the analytically pure complex was obtained as an off-white powder (2.23 g, 95 %).

Synthesis of imines 33-57 and 73-77.

METHOD A: The ketone (2.0 mmol, 1.0 equivalents), the 2-chloroaniline (2.4 mmol, 1.2 equivalents) $NaHCO_3$ (840 mg, 10 mmol, 5 equivalents), and activated molecular sieves along with 8 mL toluene were charged in a 50 mL Schlenk flask under anhydrous conditions. The reaction was then stirred for 16 hours at 90°C. After this time the mixture was filtered though celite, the solvent and the excess aniline were evaporated under reduced pressure. The imine was used without further purification.

METHOD B: The ketone (2.0 mmol, 1.0 equivalents), the 2-chloroaniline (2.4 mmol, 1.2 equivalents) p-toluene-sulphonic acid monohydrate (38 mg, 0.2 mmol, 10%) and activated molecular were charged along with 10 mL toluene into a 50 mL Schlenk flask under anhydrous conditions. The reaction was then stirred for 16 hours at 110°C. After this time the mixture was quenched with sodium carbonate, filtered though celite, the solvent and the excess aniline were evaporated under reduced pressure. The imine was used without further purification.

LARGE SCALE SYNTHESIS OF 49: A flame-dried 100 mL round bottom flask, equipped with a stirring bar and a condenser, was loaded with 30 g of activated 3Å molecular sieves, 21.2 mL of 3-pentanone (17. 3 g, 0.2 mol, 10 equivalents) and 2.1 mL of 2-chloroaniline (2.51 g, 20 mmol). The mixture was heated to reflux for 48 hours, then allowed to cool down and filtered through $MgSO_4$ washing with EtOAc, then the excess of pentanone was evaporated at the rotavapor and the traces of 2-chloroaniline removed leaving the mixture at the pump for two days at 35 °C under stirring. The desired product was obtained as a yellow liquid (2.5 g, 64%)

Optimized protocol for the cyclization of imines to indoles.

Method Cy-A: The precatalysts **42** [Pd(IPr*)(cinnamyl)Cl] (1.5 mg, 0.5 mol%), the imine **(**0.25 mmol, 1 equivalents) and NaO*t*Bu (26.4 mg, 0.28 mmol, 1.1 equiv) were weighted in a screw-cap vial equipped with a magnetic stirring bar. The vial was closed with a septum cap and purged by 3 vacuum/nitrogen cycles. Dry dioxane (2 mL) was added by syringe, and the reaction was then stirred at 110°C for 4 hr. The vessel was then allowed to cool to rt and the reaction was quenched with 3 drops of water, the organic phase was filtered through magnesium sulfate washing with ethyl acetate. The two reaction duplicates were purified together via flash chromatography to afford the pure product.

Method Cy-B: The precatalysts **42** [Pd(IPr*)(cinnamyl)Cl] (1.6 mg, 0.5 mol%), the imine (0.25 mmol, 1 equivalents) and NaO*t*Bu (26.4 mg, 0.28 mmol, 1.1 equiv) were weighted in a screw-cap vial equipped with a magnetic stirring bar. The vial was closed with a septum cap and purged by 3 vacuum/nitrogen cycles. Dry dioxane (2 mL) was added by syringe, and the reaction was then stirred at 110°C for 16 hr. The vessel was then allowed to cool to rt and the reaction was quenched with 3 drops of water, the organic phase was filtered through magnesium sulfate, washing with ethyl acetate. The two reactions duplicate were purified together via flash chromatography to afford the desired product.

Method Cy-C: The precatalysts **42** [Pd(IPr*)(cinnamyl)Cl] (5.9 mg, 2.0 mol%), the imine (0.25 mmol, 1 equivalents) and NaO*t*Bu (26.4 mg, 0.28 mmol, 1.1 equiv) were weighted in a screw-cap vial equipped with a magnetic stirring bar. The vial was closed with a septum cap and purged by 3 vacuum/nitrogen cycles. Dry dioxane (2 mL) was added by syringe, and the reaction was then stirred at 110°C for 24 hours. The vessel was then allowed to cool to rt and the reaction was quenched with 3 drops of water, the organic phase was filtered through magnesium sulfate, washing with ethyl acetate. The two reactions duplicate were purified together via flash chromatography to afford the desired product.

Large scale cyclisation: A flame dried 250 mL Schlenk flask equipped with a stirring bar was loaded with NaOtBu (1.15 g, 12 mmol, 1.2 equivalents), filled with argon and then 60 mL of dry, degassed dioxane were added. The imine (1.95 g, 10 mmol) was

weighted in a vial and added with a syringe, washing both vial and syringe with dioxane (2x5 mL). **42** [Pd(IPr*)(cinnamyl)Cl] (55 mg, 0.5 mol%) was dissolved in 5 mL of dioxane and added to the reaciton mixture with a syringe, washing with 5 mL dioxane. The flask was then immerged in a pre-heated oil bath at 110°C, stirring at 300 rpm for 24 hours. The reactor was then cooled down and the reaction was quenched with 20 mL of water and extracted with diethyl ether (4 x 20 mL). The combined organic layers where dried over $MgSO_4$, filtered and evaporated under vacuum. The crude was left unde rhigh vacuum for two hours, after which NMR analysis showed the pure product (>95 %). Isolated yield 1.31 g, 83%.

Characterisation data.

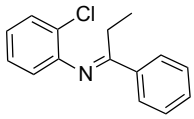
42. [Pd(IPr*)(cinnamyl)Cl]

^{1}H NMR (400 MHz, CD2Cl2): δ 7.48-7.18 (m, 25H), 7.14-7.07 (m, 12H), 6.90 (s, 4H), 6.87-6.77 (m, 8H), 5.91 (s, 2H), 5.78 (s, 2H), 5.26 (s, 2H), 5.05-4.94 (m, 1H), 4.50 (d, J = 13.4 Hz, 1H), 2.56 (d, J = 8.4 Hz, 1H), 2.25 (s, 6H), 1.16 (d, J = 12.6 Hz, 1H).

^{13}C NMR (100 MHz, CDCl3): δ 182.6, 144.6, 143.8, 141.4. 140.6, 138.4, 137.8, 135.9, 130.6 , 130.3, 129.3, 128.7, 128.4, 128.2, 127.7, 127.2, 126.5, 126.4, 123.5, 109.0, 91.3, 51.5, 47.4, 22.0.

Anal. Calcd. for $C_{78}H_{65}ClN_2Pd$: C, 79.92; H, 5.59; N, 2.39. Found: C, 80.09; H, 5.46; N, 2.29.

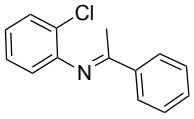
33. *N*-(2-Chlorophenyl)-1-phenylpropan-1-imine:



Method A. Yield 61 %, 302 mg, brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ. 7.99 (m, 2H), 7.52-7.45 (m, 3H9, 7.43 (d,d, J= 8.0, 1.2 Hz, 1H), 7.25 (td, J= 7.6, 1.2 Hz, 1 H), 7.03 (td, J= 8.0, 1.6 Hz, 1 H), 6.83 (dd, J= 8.0, 1.6 Hz, 1H), 2.63 (q, J= 7.6 Hz, 2H), 1.08 (t, J= 7.6 Hz, 3H)

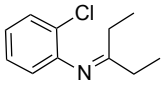
48. *N*-(2-Chlorophenyl)-1-phenylethan-1-imine:



Method A. Yield 77%, 353 mg, brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ. 8.05-8.01 (m, 2H), 7.51-7.47 (m, 3H), 7.43 (dd, J= 8.0, 1.2 Hz, 1H), 7.26 (dd, J= 7.6, 1.2 Hz, 1H), 6.84 (dd, J= 7.6, 1.2 Hz, 1H),, 2.22 (s, 3H).

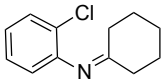
49. *N*-(2-Chlorophenyl)pentan-3-imine:



Method A. Yield 69%, 272 mg, yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, J= 8.0, 1.4 Hz, 1H), 7.17 (td, J= 7.6, 1.4 Hz, 1H), 6.96 (td, J= 8.0, 7.4, 1.6 Hz, 1H), 6.71 (dd, J= 7.9, 1.6 Hz, 1H), 2.50 (q, J= 7.4 Hz, 2H), 2.09 (q, J= 7.7 Hz, 2H), 1.08-1.02 (m, 6H).

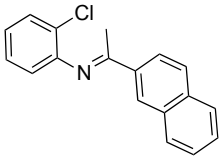
50. *N*-(2-Chlorophenyl)cyclohexanimine:



Method A. Yield 65%, 270 mgrown oil, b.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, J= 8.0, 1.4 Hz, 1H), 7.17 (td, J= 7.6, 1.4 Hz, 1H), 6.97 (ddd, J= 8.0, 7.4, 1.6 Hz, 1H), 6.74 (dd, J= 7.8, 1.6 Hz, 1H), 2.55-2.49 (m, 2H), 2.11-2.04 (m, 2H), 1.92-1.82 (m, 2H), 1.67 (p, J= 3.1 Hz, 4H).

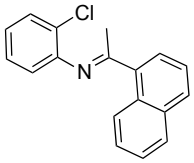
51. *N*-(2-Chlorophenyl)-1-(naphthalen-2-yl)ethan-1-imine:



Method A. Yield 76%, 425 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44-8.37 (m, 1H), 8.26 (dd, J= 8.7, 1.8 Hz, 1H), 8.00-7.85 (m, 3H), 7.61-7.50 (m, 2H), 7.45 (dd, J= 8.0, 1.4 Hz, 1H), 7.32-7.24 (m, 1H), 7.05 (dt, J= 8.1, 7.4, 1.6 Hz, 1H), 6.87 (dd, J= 7.9, 1.6 Hz, 1H), 2.33 (s, 3H).

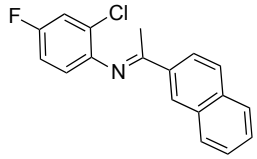
52. *N*-(2-Chlorophenyl)-1-(naphthalen-1-yl)ethan-1-imine:



Method B. Yield 69%, 390 mg, pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ. 8.6 (d, J=8.8 Hz, 1H), 7.92 (m, 2H), 7.71 (d, J= 8.8 Hz, 1H), 7.61 (td, J= 6.8, 1.2 HZ, 1H), 7.57 (t, J= 8.0 HZ, 2H), 7.50 (dd, J= 8.0, 0.9 HZ, 1H), 7.32 (dd, J= 7.6, 1.2 Hz, 1H), 7.09 (ddd, J= 8, 7.5, 1.6 Hz, 1H), 7.00 (dd, J= 7.8, 1.5 Hz, 1H), 2.36 (s, 3H).

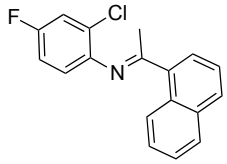
53. *N*-(2-Chloro-4-fluorophenyl)-1-(147aphthalene-2-yl)ethan-1-imine:



Method A. Yield 58%, 345 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43-8.34 (m, 1H), 8.23 (dd, J= 8.6, 1.8 Hz, 1H), 8.01-7.83 (m, 3H), 7.63-7.50 (m, 2H), 7.21 (dd, J= 8.4, 2.7 Hz, 1H), 7.02 (ddd, J= 8.7, 8.0, 2.8 Hz, 1H), 6.82 (dd, J= 8.8, 5.6 Hz, 1H), 2.33 (s, 3H).

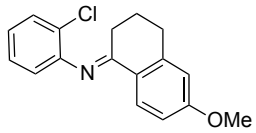
54. *N*-(2-Chloro-4-fluorophenyl)-1-(naphthalen-1-yl)ethan-1-imine:



Method B. Yield 56%, 388 mg, pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 8.4 Hz, 1H), 7.92 (t, *J* = 7.0 Hz, 2H), 7.81 (dd, J = 12.2, 8.1 Hz, 1H), 7.68 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.59 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.26 (dd, J=8.4, 2.8 Hz, 1H) 7.05 (ddd, *J* = 8.7, 8.0, 2.7 Hz, 1H), 6.97-6.93 (m, 1H), 6.48-6.37 (m, 1H), 2.32 (s, 3H).

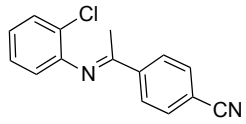
55. *N*-(2-Chlorophenyl)-6-methoxy-3,4-dihydronaphthalen-1(2H)-imine:



Method B. Yield 70%, 402 mg, brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (d, J= 8.8 Hz, 1H), 7.39 (dd, J= 8.0, 1.4 Hz, 1H), 7.22 (td, J= 7.6, 1.4 Hz, 1H), 6.99 (ddd, J = 8.1, 7.4, 1.6 Hz, 1H), 6.86 (dd, J= 8.8, 2.7 Hz, 1H), 6.81 (dd, J= 7.9, 1.6 Hz, 1H), 6.70 (d, J= 2.5 Hz, 1H), 3.86 (s, 3H), 2.88 (t, J= 6.1 Hz, 2H), 2.45-2.35 (m, 2H), 1.99-1.88 (m, 2H).

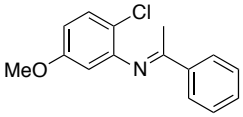
56. 4-(1-((2-Chlorophenyl)imino)ethyl)benzonitrile:



Method A. Yield 69%, 354 mg, yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.08 (m, 2H), 7.79-7.73 (m, 2H), 7.43 (dd, J= 8.0, 1.3 Hz, 1H), 7.27 (m, 1H), 7.07 (ddd, J= 8.0, 7.4, 1.6 Hz, 1H), 6.80 (dd, J= 7.9, 1.5 Hz, 1H), 2.22 (s, 3H).

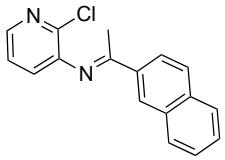
57. 2-Chloro-5-methoxy-*N*-(1-phenylethylidene)aniline:



Method B. Yield 70%, 362 mg, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-7.98 (m, 2H), 7.51-7.43 (m, 3H), 7.29 (d, J= 8.0 Hz, 1H), 6.60 (dd, J= 8.8, 3.0 Hz, 1H), 3.79 (S, 3H), 2.22 (s, 3H).

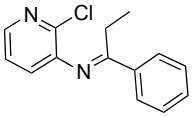
73. 2-Chloro-*N*-(1-(naphthalen-2-yl)ethylidene)pyridin-3-amine:



Method B. Yield 55%, 341 mg, brown solid.

^{1}H NMR (400 MHz, CDCl3): δ 11.94-11.99 (s. 1H), 8.47-8.51 (S,1H), 8.33-8.37 (dd, J= 4.8Hz, 1.6Hz 1H), 8.07-8.13 (dd, J= 8.8, 2.0Hz 1H), 7.93-8.06(m, 3H), 7.77-7.83 (m, 2H), 7.52-7.62 (m, 2H), 7.22-7.25(m, 1H), 7.10-7.16 (m, 1H).

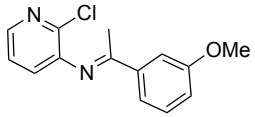
74. 2-Chloro-*N*-(1-phenylpropylidene)pyridine-3-amine:



Method A. Yield 66%, 323 mg, brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.13 (m, 1H), 7.96 (d, J= 6.8 Hz, 2H), 7.49 (m, 3H), 7.23 (m, 1H), 7.14 (m, 1H), 2.61 (q, J= 7.6 Hz, 2H), 1.08 (t, J= 7.6 Hz, 3H).

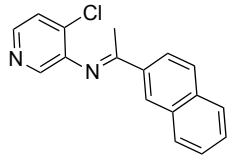
75. 2-Chloro-*N*-(1-(3-methoxyphenyl)ethylidene)pyridin-3-amine:



Method B. Yield 77%, 477 mg, yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16-8.19 (dd, J= 4.5, 2Hz, 1H), 7.60-7.65 (m, 1H), 7.53-7.57 (m, 1H), 7.38-7.43 (t, J= 8Hz, 1H), 7.24-7.30 (m, 1H), 7.16-7.21 (dd, J=7.5, 1.5Hz, 1H), 7.06-7.11 (m , 1H),), 3.90 (s, 3H), 2.23 (s, 3H).

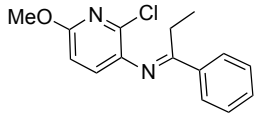
76. 4-Chloro-*N*-(1-(naphthalen-2-yl)ethylidene)pyridin-3-amine:



Method B. Yield 45%, 268 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40-8.45 (s, 1H), 8.17-8.33 (m, 3H), 7.88-8.02 (m, 3H), 7.54-7.63 (m, 2H), 7.40-7.45 (d, 5.2Hz, 1H), 2.37-2.41 (S, 3H).

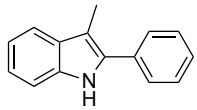
77. 2-Chloro-6-methoxy-*N*-(1-phenylpropylidene)pyridin-3-amine:



Method B. Yield 52%, 286 mg, brown solid.

^{1}H NMR (400 MHz, CDCl3): δ 7.95-7.99 (m, 2H), 7.46-7.53 (m, 3H), 7.11-7.15 (d, 8.4Hz, 1H), 6.71-6.76 (d, 8.4Hz, 1H), 3.95-4.00 (s, 3H), 2.60-2.69 (q, 7.6Hz, 2H), 1.05-1.13 (t, 7.6Hz, 3H).

34. 3-Methyl-2-phenyl-1H-indole:[10]



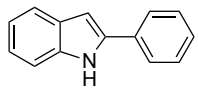
Method Cy-A. Yield 91%, 94 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ. 8.01 (bs, 1H), 7.65-7.57 (m, 3H), 7.49 (t, J= 7.7 Hz, 2H), 7.40-5.33 (m, 2H), 7.22 (ddf, J= 8.1, 7.1, 1.3 Hz, 1H), 7.16 (1H, ddd, J= 8.1, 7.5, 1.1 Hz), 2.48 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 134.0, 133.3, 130.0, 128.8, 127.7, 127.3, 122.3, 119.5, 118.9, 110.6, 108.7, 9.6.

Analytical data matches previously reported characterisation.

60. 2-Phenyl-1*H*-indole:[10]



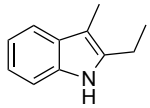
Method Cy-A. Yield 86%, 83 mg, brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.67 (ddd, J= 8.1, 7.2, 1.3 Hz, 3H), 7.46 (t, J= 7.7 Hz, 2H), 7.41 (dd, J= 8.1, 1.0 Hz, 1H), 7.37-7.32 (m, 1H), 7.25-7.20 (m, 1H), 7.19-7.11 (m, 1H), 6.85 (dd, J= 2.2, 0.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.9, 136.8, 132.4, 129.3, 129.1, 127.8, 125.2, 122.4, 120.7, 120.3, 110.9, 100.0.

Analytical data matches previously reported characterisation.

61. 2-Ethyl-3-methyl-1*H*-indole:[11]



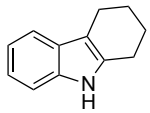
Method Cy-B. Yield 80%, 64 mg, brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.52 (ddd, J= 7.4, 1.8, 0.8 Hz, 1H), 7.29 (dt, J= 8.0, 0.9 Hz, 1H), 7.18-7.08 (m, 2H), 2.77 (q, J= 7.6 Hz, 2H), 2.27 (s, 3H), 1.29 (t, J= 7.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.5, 135.1, 129.4, 120.9, 119.0, 118.1, 110.0, 106.2, 19.4, 14.1, 8.4.

Analytical data matches previously reported characterisation.

62. 2,3,4,9-Tetrahydro-1*H*-carbazole:[11]



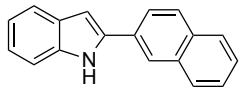
Method Cy-C. Yield 82%, 70 mg, brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.52-7.47 (m, 1H), 7.27 (d, J= 8.0 Hz, 1H), 7.12 (m, 2H), 2.74 (q, J= 6.3 Hz, 4H), 2.00-1.85 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 134.1, 127.8, 121.0, 119.1, 117.7, 110.3, 110.2, 23.3, 23.3, 23.2, 20.9.

Analytical data matches previously reported characterisation.

63. 2-(Naphthalen-2-yl)-1*H*-indole:[12]



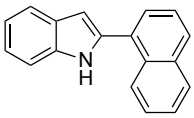
Method Cy-B. Yield 84%, 102 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 8.06 (d, J= 1.7 Hz, 1H), 7.95-7.80 (m, 4H), 7.71-7.63 (m, 1H), 7.57-7.41 (m, 3H), 7.23 (ddd, J= 8.2, 7.1, 1.2 Hz, 1H), 7.15 (ddd, J= 8.0, 7.1, 1.1 Hz, 1H), 6.99-6.93 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 137.0, 133.6, 132.9, 129.7, 129.4, 128.8, 128.0, 127.8, 126.7, 126.2, 123.8, 123.1, 122.6, 120.8, 120.4, 110.9, 100.7.

Analytical data matches previously reported characterisation.

64. 2-(Naphthalen-1-yl)-1*H*-indole:[12]



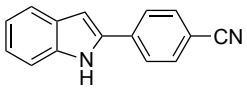
Method Cy-A. Yield 80%, 97 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38-8.17 (m, 2H), 7.98-7.86 (m, 2H), 7.73 (m, 1H), 7.65 (dd, J= 7.1, 1.3 Hz, 1H), 7.60-7.49 (m, 3H), 7.45 (m, 1H), 7.31-7.17 (m, 2H), 6.82 (dd, J= 2.1, 0.9 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 136.7, 136.4, 134.0, 131.6, 131.1, 128.9, 128.6, 128.5, 127.2, 126.7, 126.2, 125.7, 125.4, 122.2, 120.7, 120.2, 110.9, 103.7.

Analytical data matches previously reported characterisation.

65. 4-(1*H*-Indol-2-yl)benzonitrile:[13]



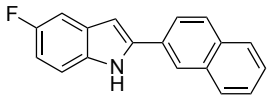
Method Cy-C. Yield 52%, 57 mg, yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.72 (q, J= 8.4 Hz, 4H), 7.66 (dd, J= 8.0, 1.0 Hz, 1H), 7.43 (dq, J= 8.2, 0.9 Hz, 1H), 7.29-7.23 (m, 1H), 7.16 (ddd, J= 8.0, 7.1, 1.0 Hz, 1H), 6.96 (dd, J= 2.2, 0.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 136.6, 135.5, 132.9 (X2), 128.9, 125.3 (X2), 123.7, 121.4, 120.8, 118.9 (X2), 111.3, 110.5, 102.6.

Analytical data matches previously reported characterisation.

66. 5-Fluoro-2-(naphthalen-2-yl)-1*H*-indole:[14]



Method Cy-C. Yield 84%, 110 mg, brown solid.

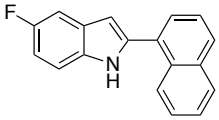
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (s, 1H), 8.05 (d, J= 1.7 Hz, 1H), 7.93-7.83 (m, 3H), 7.80 (dd, J= 8.5, 1.8 Hz, 1H), 7.51 (m, 2H), 7.32 (m, 2H), 6.96 (td, J= 9.0, 2.5 Hz, 1H), 6.91 (dd, J= 2.1, 0.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 157.1, 139.6, 133.5 (X2), 133.0, 12945, 128.9, 128.0, 127.8, 126.8, 126.3, 123.7, 123.3, 111.5 (d, *J*= 9.7 Hz), 110.8 (d, *J*= 26.3 Hz), 105.5 (d, *J*= 23.5 Hz), 100.7 (d, *J*= 4.7 Hz).

^{19}F NMR (376.6 MHz, $CDCl_3$): δ -124.07.

Analytical data matches previously reported characterisation.

67. 5-Fluoro-2-(naphthalen-1-yl)-1*H*-indole:



Method Cy-C. Yield 9%,118 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.34(m, 2H), 7.91-7.99(m, 2H), 7.62-7.66(dd, 1H 7.8hz & 1.8hz), 7.56-7.61(m, 3H), 7.33-7.42(m, 2H), 7.00-7.07 (m, 2H), 6.78-6.8 (dd 2.4hz & 1.2hz , 1H)

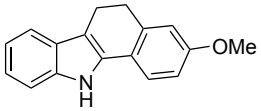
^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 157.2 , 138.5 , 133.9 , 132.9 , 131.4 , 130.7 , 129.2 (d, Cq), 128.9 , 128.6 , 127.3 , 126.8 , 126.3 , 125.6 , 125.4 , 111.49 (d, 9.5hz, CH), 110.54 (d, *J*= 28.7 Hz), 105.39 (d, *J*= 23.7Hz), 103.8 (d, *J*=5Hz).

^{19}F NMR (376.6 MHz, $CDCl_3$): δ -118.90.

HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $[C_{18}H_{13}FN]^+$, 262.1027 ; found, 262.1029.

Analytical data matches previously reported characterisation.

68. 3-Methoxy-6,11-dihydro-5*H*-benzo[a]carbazole:[15]



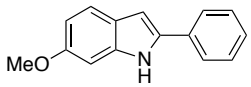
Method Cy-C. Yield 90%, 112 mg, brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.54 (dd, J= 7.5, 1.4 Hz, 1H), 7.41-7.31 (m, 1H), 7.24 (d, J= 8.3 Hz, 1H), 7.15 (m, 2H), 6.88 (d, J= 2.6 Hz, 1H), 6.79 (dd, J= 8.3, 2.6 Hz, 1H), 3.84 (s, 3H), 3.05 (dd, J= 8.6, 6.5 Hz, 2H), 3.01-2.94 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6, 138.6, 136.8, 133.2, 127.6, 122.2, 121.8, 120.9, 119.82, 118.4, 114.9, 111.3, 111.0, 110.8, 55.4, 30.0, 19.7.

Analytical data matches previously reported characterisation.

69. 6-Methoxy-2-phenyl-1*H*-indole:[13]



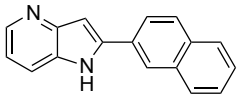
Method Cy-C. Yield 72%, 80 mg, yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (br s, 1H), 7.21 (d,J= 7.5 Hz, 2H), 7.50 (d,J= 8.5 Hz, 1H), 7.44 (t,J= 7.5Hz, 2H),7.24–7.30(m, 1H), 6.90 (d, J= 2.2 Hz, 1H), 6.80 (dd,J= 6.5, 2.0 Hz, 1H), 6.76 (d, J = 1.4 Hz, 1H), 3.87 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ156.7, 137.6 (X2), 136.8, 132.5, 129.0, 127.2, 124.7 (X2), 123.6, 121.3, 110.2, 99.8, 94.5, 55.7.

Analytical data matches previously reported characterisation.

80. 2-(Naphthalen-2-yl)-1*H*-pyrrolo[3,2-*b*]pyridine:



Method Cy-C. Yield 74%, 94 mg, brown solid.

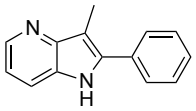
Method Cy-C afforded 90 mg, 74% of the desired product as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): 11.94-11.99 (s. 1H) 8.47-8.51 (S,1H), 8.33-8.37 (dd, 4.8Hz & 1.6Hz 1H), 8.07-8.13 (dd,8.8Hz & 2.0Hz 1H), 7.93-8.06(m, 3H), 7.77-7.83 (m, 2H), 7.52-7.62 (m, 2H), 7.22-7.25(m, 1H), 7.10-7.16 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4 , 143.5, 141.3, 133.6 , 133.1 , 130.8, 129.6, 129,2, 128.5, 128.2, 127.4 , 126.9 , 124.4 , 124.5 , 118.5 , 117.5 , 100.5.

HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $[C_{17}H_{13}N_2]^+$, 245.1073 ; found, 245.1073.

81. 3-Methyl-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine[16]



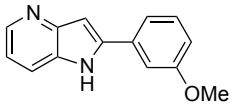
Method Cy-B Yield 80%, 83 mg, brown solid.

^{1}H NMR (400 MHz, CD_3OD_3): δ 8.27 (dd, J= 4.8, 1.2 Hz, 1H), 7.76 (dd, J= 8.0, 1.2 Hz, 1H), 7.71-7.65 (m, 2H), 7.50 (t, J= 7.6 Hz, 2H), 7.39 (t, J= 7.6 Hz, 1H), 7.14 (dd, J= 8.0, 4.8 Hz, 1H), 2.50 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 142.4, 140.0, 134.0, 131.2, 129.8, 129.1, 119.9, 117.7, 108.4, 19.0.

Analytical data matches previously reported characterisation.

82. 3-Methyl-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine:



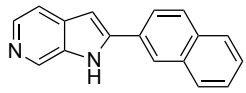
Method Cy-C. Yield 87%, 97 mg, off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16-8.19 (dd, 4.5hz & 2Hz, 1H), 7.60-7.65 (m, 1H), 7.53-7.57 (m, 1H), 7.38-7.43 (t, 8Hz, 1H), 7.24-7.30 (m, 1H), 7.16-7.21 (dd, 7.5Hz & 1.5Hz, 1H), 7.06-7.11 (m , 1H), 3.89-3.91 (s, 3H), 2.22-2.25 (S, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 159.7, 144.8 , 144.2 , 141.3 , 139.8 , 129.5 , 128.6 , 122.9 , 120.1 , 117.5 , 112.2 , 55.5, 18.5.

HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $[C_{14}H_{13}N_2O]^+$, 225.1022 ; found, 225.1021.

83. 2-(Naphthalen-2-yl)-1*H*-pyrrolo[2,3-*c*]pyridine:



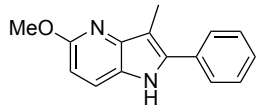
Method Cy-C. Yield 88%, 98 mg, brown solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1-12.5 (s, 1H), 8.80-8.84 (s, 1H), 8.49-8.53 (s, 1H), 8.02-8.15 (m, 3H), 7.94-8.01(m, 2H), 7.54-7.62 (m, 3H), 7.12-7.16(s, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 142.0 , 138.5 , 134.8 , 134.5 , 133.5 , 133.4 , 133.3 , 129.2 , 129.1 , 128.3 , 128.1 , 127.2 , 127.0 , 124.9 , 124.5 , 115, 99.9.

HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $[C_{17}H_{13}N_2]^+$, 245.1073 ; found, 245.1071.

84. 5-Methoxy-3-methyl-2-phenyl-1*H*-pyrrolo[3,2-*b*]pyridine:



Method Cy-A. Yield 87%, 104 mg, yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.07 (s, 1H), 7.60-7.65 (m, 2H), 7.54-7.58 (d, 8.8Hz, 1H), 7.47-7.54 m, 2H), 7.36-7.42 (m, 1H), 6.61-6.65 (d, 8.8Hz, 1H), 4.06-4.08 (S, 3H), 2.52-2.55 (S, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9 , 143.8, 136.4 , 133.2 , 128.9 , 127.6 , 127.3 , 124.7 , 121.2 , 109.4 , 105.4 , 53.3 (CH3), 8.7 (CH3).

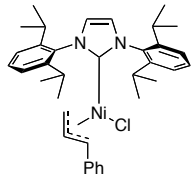
HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $[C_{15}H_{14}N_2O]^+$, 239.1179; found, 239.1178.

7.4 Experimental details for Chapter 4

Synthesis and characterization of the [Ni(NHC)(cin)Cl] complexes 40-43.[17]

The complexes were synthesized following a reported procedure. Inside a glovebox, $[Ni(COD)_2]$ (275 mg, 1.0 mmol) was suspended in cyclooctadiene (0.5 ml) in a 100 ml Schlenk flask. Cinnamyl chloride (152.6 mg, 1.0 mmol) was added dropwise while stirring, and fast appearance of a dark red colour was observed. After ten minutes, a solution of the selected NHC free ligand (1 mmol) in THF (10 ml) was added. After one hour, the brown solution was filtered through a plug of celite, and concentrated under vacuum. The brown solid were suspended and scratched in hexane twice, and after evaporation a yellow/orange powder was obtained.

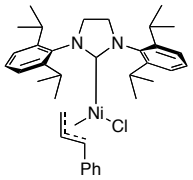
40. [Ni(IPr)(cinnamyl)Cl]:[17]



Yield 81%, 424 mg.

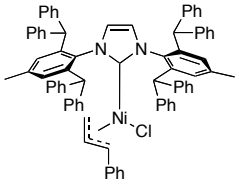
^{1}H-NMR (300 MHz, Benzene-d_6): δ 7.10-7.27 (m, 7H), 7.02 (m, 2H), 7.0 (m, 2H), 6.58 (s, 2H), 5.0 (ddd, J = 12.8, 12.8, 6.8 Hz, 1H), 3.6 (d, J = 13.2 Hz, 1H), 3.2 (m, 2H), 3.0 (m, 2H), 2.4 (d, J = 6.9 Hz, 1H), 1.49 (d, J = 6.7 Hz, 6H), 1.33 (d, J = 6.7 Hz, 6H), 1.01 (m, 13H).
^{13}CNMR (75 MHz, Benzene-d_6): δ 188.4, 146.8, 146.7, 140.4, 136.4, 130.3, 128.5, 125.9, 124.6, 124.1, 102.7, 83.9, 41.9, 28.9, 28.8, 26.5, 26.4, 23.0, 22.9, 22.7.
Anal. Calc. for $C_{36}H_{45}ClN_2Ni$: C, 72.08; H, 7.56; N, 4.67. Found: C, 71.97; H, 7.46; N, 4.55.

41. [Ni(SIPr)(cinnamyl)Cl]:



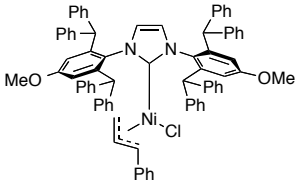
Yield 75%, 394 mg.
^{1}H NMR (400 MHz, Benzene-d_6): δ 7.25-7.18 (m, 6H), 7.16-7.07 (m, 3H), 7.03-6.96 (m, 2H), 4.93 (td, *J* = 12.9, 6.9 Hz, 1H, H_{cin}), 3.63 (d, *J* = 13.2 Hz, 1H, H_{cin}), 3.51 (s, 2H), 2.45 (dd, *J* = 6.9, 1.6 Hz, 1H, H_{cin}), 1.58-1.53 (m, 6H), 1.39 (d, *J* = 6.6 Hz, 6H), 1.20 (dd, *J* = 12.7, 1.4 Hz, 1H, H_{cin}), 1.13 (d, *J* = 6.9 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H).
^{13}C NMR (100 MHz, Benzene-d_6): δ 217.8, 139.8, 136.5, 129.2, 128.0, 127.9, 127.6, 125.6, 124.2, 102.7, 85.2, 53.5, 41.4, 28.4, 26.5, 23.3.
Anal. Calc. for $C_{36}H_{47}ClN_2Ni$: C, 71.83; H, 7.87; N, 4.65. Found: C, 71.93; H, 7.91; N, 4.61.

42. [Ni(IPr*)(cinnamyl)Cl]:



Yield 83%, 870 mg.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.00 (m, 36H), 6.98-6.73 (m, 13H), 6.21 (s, 2H), 5.85 (s, 2H), 5.66-5.64 (m, 1H, H_{cin}), 5.21 (s, 2H), 5.03 (s, 1H, H_{cin}), 4.04 (d, *J* = 13.5 Hz, 1H, H_{cin}), 2.49-2.20 (m, 6H), 1.02-0.84 (m, 1H, H_{cin}).
^{13}C NMR (100 MHz, $CDCl_3$): δ 183.1, 144.6, 144.5, 143.9, 142.6, 142.0, 141.5, 140.7, 140.6, 139.4, 138.4, 136.1, 130.9, 130.9, 130.6, 130.5, 129.9, 129.9, 129.9, 129.4, 129.3, 128.9, 128.8, 128.7, 128.7, 128.4, 128.4, 128.3, 128.3, 127.9, 127.2, 127.1, 126.5, 126.5, 126.4, 126.4, 126.3, 124.2, 123.8, 103.4, 86.5, 51.6, 51.5, 51.4, 41.6, 28.2, 22.0.
Anal. Calc. for $C_{78}H_{65}ClN_2Ni$: C, 83.31; H, 5.83; N, 2.49. Found: C, 83.16; H, 5.85; N, 2.61.

43. [Ni(IPr*^{OMe})(cinnamyl)Cl]:



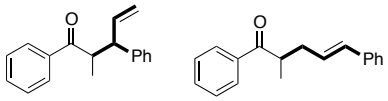
Yield 83%, 896 mg.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H), 7.37-7.27 (m, 14H), 7.24-7.15 (m, 11H), 7.11-7.05 (m, 12H), 6.86-6.74 (m, 8H), 6.15 (s, 2H), 5.86 (s, 2H), 5.11 (s, 2H), 5.06 (m, 1H, H_{cin}) 4.06 (d, J = 13.6 Hz, 1H, H_{cin}), 3.67 (s, 6H), 2.22 (d, J = 6.8, 1H, H_{cin}), 0.97 (d, J = 12.4, 1H, H_{cin}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 183.7, 158.9, 144.3, 144.2, 143.7, 143.7, 143.5, 142.7, 142.4, 141.4, 139.4, 131.7, 130.5, 129.9, 129.3, 129.2, 128.9, 128.8, 128.4, 128.4, 127.9, 127.3, 127.2, 126.6, 126.6, 126.4, 126.4, 123.9, 115.7, 115.3, 115.2, 103.4, 86.5, 55.2, 51.7, 51.7, 41.7, 28.2.

Anal. Calc. for $C_{78}H_{66}ClN_2NiO_2$: C, 81.01; H, 5.66; N, 2.42. Found: C, 80.91; H, 5.48; N, 2.49.

Isolation of the activation product 75+75´:



In a vial fitted with a screw cap, in the glove box, complex **42** (0.1 mmol) and NaO*t*Bu (19.2 mg, 0.2 mmol) were dissolved in 3 mL of toluene, and the vial was then closed with a septum cap THF (0.5 mL). Outside the glovebox, propiophenone (0.2 mmol) was added *via* a syringe. The solution was stirred overnight at 60°C. The reaction was cooled down to room temperature and the vial was introduced in the glovebox. The solvent was evaporated under vacuum. The crude was then extracted with pentane (3 x 5 mL). The combined organic phases of were taken out of the glovebox and filtered through a pad of celite. The solvent was then evaporated under vacuum and the crude was purified by flash chromatography (pentane:AcOEt = 100:1) to afford an unseparable mixture of **75**/**75´** (75/25) in 84% yield.

^{1}H NMR (500 MHz, $CDCl_3$) **5**: δ 8.03-7.97 (m, 2H), 7.61-7.55 (m, 1H), 7.53-7.46 (m, 2H), 7.38-7.29 (m, 3H), 7.28-7.22 (m, 2H), 5.95 (ddd, J = 17.1, 10.3, 7.4 Hz, 1H), 5.03-4.85 (m, 2H), 3.97-3.84 (m, 1H), 3.84-3.74 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8 (**5**), 203.7 (**5´**), 141.8, 140.0, 137.5, 137.3, 136.5, 133.2, 133.1, 132.1, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 127.7, 127.2, 126.8, 126.2, 115.7, 52.9 (**5**), 45.1 (**5**), 41.1 (**5´**), 37.0 (**5´**), 17.4 (**5´**), 17.1 (**5**).

HRMS (EI+): *m*/*z* calculated for $C_{18}H_{19}O$: 251.1433, found $[M+H]^+$: 251.1430.

General procedure for the Ni-catalysed arylation of ketones:

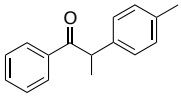
Inside a glovebox, [Ni(IPr*)(cin)Cl] **42** (0.015 mmol, 16.9 mg) and NaO*t*Bu (96 mg, 1 mmol), were put in a screw cap vial equipped with a stirring bar. Aryl chloride (0.5 mmol) and/or ketone (1.0 mmol) were added at this stage, if solid. The vial was then sealed. Outside the glovebox, the solvent (toluene, 2 mL) and the aryl chloride and/or the ketone were added, if liquid. The reaction was then stirred for 16 hours at 80°C. The reaction was quenched adding some drops of water and filtered through magnesium sulphate. After checking the gas chromatogram conversion, the crude was absorbed on silica and purified by flash chromatography (typically with a *n*-hexane:AcOEt = 9:1) to afford the desired product.

Procedure for the synthesis of compound 79:

Inside a glovebox, [Ni(IPr*^{OMe})(cinnamyl)Cl] **43** (2 mol%, 0.103 mmol, 119 mg), 6-methoxytetralone (1.00 g, 5.68 mmol, 1.1 equivalents) and NaO*t*Bu (992 mg, 10.32 mmol, 2.0 equivalents), were put in a 100 ml Schlenk flask equipped with a stirring bar. The Schlenk was then closed with a septum cap. Outside the glovebox, the solvent (toluene, 10 mL) and chlorobenzene (5.16 ml, 5.16 mmol, 1 equivalents) were added via syringe. The reaction was stirred for 16 hours at 100°C, at 500 rpm in an oil bath. The reaction was quenched adding 10 ml of water and exctracted with ethyl acetate (3x10 mL). The organic phase was concentrated was dried over magnesium sulphate and the volatiles were evaporated. The crude was crystallized from ethyl acetate / hexane to afford 1.075 g of the desired product (82% yield) as a yellow solid.

Characterisation data.

48. 2-(4-Methylphenyl)-1-phenylpropan-1-one:[4]

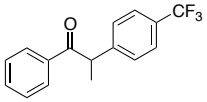


Yield 90%, 202 mg, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 7.3, 1.2 Hz, 2H), 7.50-7.44 (m, 1H), 7.44-7.34 (m, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 4.67 (q, *J* = 6.8 Hz, 1H), 2.30 (s, 3H), 1.54 (dd, *J* = 6.8, 1.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 138.6, 136.6, 136.6, 132.8, 129.8, 128.8, 128.6, 127.7, 47.6, 21.1, 19.6.

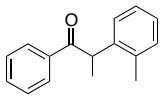
49. 1-Phenyl-2-(4-(trifluoromethyl)phenyl)propan-1-one:



Yield 55%, 153 mg.

For characterisation, see entry **43**, **Chapter 2**.

50. 2-(*p*-Tolyl)-1-phenylpropan-1-one:[19]

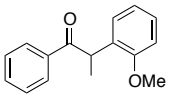


Yield 60%, 135 mg.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.50-7.42 (m, 1H), 7.39-7.32 (m, 2H), 7.24-7.19 (m, 1H), 7.15-7.01 (m, 3H), 4.78 (q, *J* = 6.8 Hz, 1H), 2.51 (s, 3H), 1.49 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 140.2, 136.7, 134.6, 132.7, 131.1, 128.6, 128.6, 127.1, 127.0, 126.9, 44.7, 19.7, 18.1.

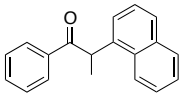
51. 2-(2-Methoxyphenyl)-1-phenylpropan-1-one:



Yield 68%, 163 mg.

For characterisation, see entry **38**, **Chapter 2**.

51. 2-(Naphthalen-1-yl)-1-phenyl-propan-1-one:[6]



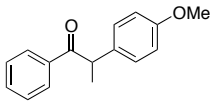
Yield 77%, 200 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34-8.25 (m, 1H), 7.97-7.87 (m, 3H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.71-7.62 (m, 1H), 7.62-7.53 (m, 1H), 7.46-7.40 (m, 1H), 7.41-7.32 (m, 2H), 7.35-7.26 (m, 2H), 7.27-7.23 (m, 1H), 5.43 (q, *J* = 6.8 Hz, 1H), 1.68 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 138.0, 136.4, 134.4, 132.74, 130.6, 129.3, 128.8, 128.6, 128.5, 128.5, 127.6, 126.7, 125.9, 125.8, 125.1, 122.6, 43.7, 18.6.

Analytical data matches previously reported characterisation.

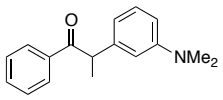
53. 2-(4-Methoxyphenyl)-1-phenylpropan-1-one:



Yield 83%, 199 mg.

For characterisation, see entry **39**, **Chapter 2**.

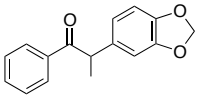
54. 2-(3-(Dimethylamino)phenyl)-1-phenylpropan-1-one:



Yield 82%, 208 mg.

For characterisation, see entry **44**, **Chapter 2**.

55. 2-Benzo[1,3]dioxol-5-yl-1-phenyl-propan-1-one:[18]



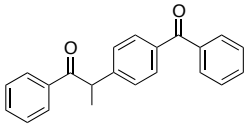
Yield 89%, 226 mg, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.54-7.44 (m, 1H), 7.45-7.33 (m, 2H), 6.82-6.67 (m, 3H), 5.94-5.86 (m, 2H), 4.61 (q, *J* = 6.8 Hz, 1H), 1.50 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.3, 148.2, 146.6, 136.6, 135.3, 132.9, 128.9, 128.6, 121.1, 108.8, 108.2, 101.1, 47.5, 19.7.

Analytical data matches previously reported characterisation.

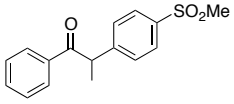
56. 2-(4-Benzoylphenyl)-1-phenylpropan-1-one:



Yield 89%, 279 mg.

For characterisation, see entry **47**, **Chapter 2**.

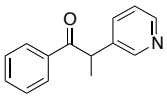
57. 2-(4-(Methylsulfonyl)phenyl)-1-phenylpropan-1-one:



Yield 65%, 187 mg.

For characterisation, see entry **46**, **Chapter 2**.

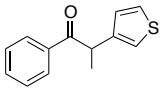
58. 1-Phenyl-2-(pyridin-3-yl)propan-1-one:



Yield 63%, 133 mg.

For characterisation, see entry**42**, **Chapter 2**.

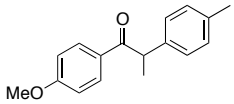
59. 1-Phenyl-2-(thiophen-3-yl)propan-1-one:



Yield 61%, 132 mg.

For characterisation, see entry **41**, **Chapter 2**.

62. 1-(4-Methoxyphenyl)-2-(4-methylphenyl)-propan-1-one:[19]



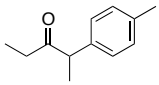
Yield 79%, 201 mg, white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.10 (dd, *J* = 8.1, 0.9 Hz, 2H), 6.88-6.83 (m, 2H), 4.61 (q, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 2.28 (s, 3H), 1.50 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 199.1, 163.2, 139.0, 136.5, 131.2, 129.7, 129.6, 127.7, 113.7, 55.5, 47.2, 21.1, 19.7.

Analytical data matches previously reported characterisation.

64. α-(4-Methylphenyl)pentan-3-one:[19]



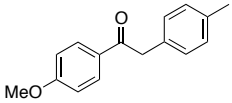
Yield 63%, 139 mg, dark yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 – 7.07 (m, 4H), 3.73 (q, *J* = 7.0 Hz, 1H), 2.46-2.34 (m, 2H), 2.33 (s, 3H), 1.38 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 211.8, 138.0, 136.8, 129.6, 127.8, 52.4, 34.3, 21.14, 17.7, 8.1.

Analytical data matches previously reported characterisation.

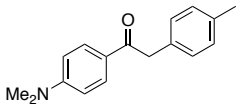
68. 1-(4-Methoxyphenyl)-2-(*p*-tolyl)ethan-1-one:



Yield 86%, 207 mg.

For characterisation, see entry **30**, **Chapter 2**.

69. 1-(4-(Dimethylamino)phenyl)-2-(*p*-tolyl)ethan-1-one:



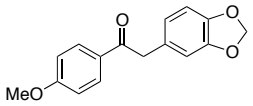
Yield 67%, 170 mg, green solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.88 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.75-6.58 (m, 2H), 4.15 (s, 2H), 3.04 (s, 6H), 2.31 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.1, 153.5, 136.1, 132.8, 131.0, 129.37, 129.3, 124.6, 110.8, 44.7, 40.1, 21.2.

HRMS (EI+): *m*/*z* calcd for $C_{17}H_{20}NO$: 254.1539, found $[M+H]^+$: 254.1539.

70. 2-(Benzo[*d*][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)ethanone:



Yield 78%, 211 mg, white solid.

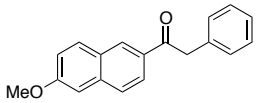
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 9.0 Hz, 2H), 6.95-6.89 (m, 2H), 6.78-6.72 (m, 2H), 6.72-6.69 (m, 1H), 5.92 (s, 2H), 4.14 (s, 2H), 3.86 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.3, 163.6, 147.9, 146.6, 131.0, 129.6, 128.6, 122.6, 113.9, 109.9, 108.5, 101.1, 55.6, 44.9.

HRMS (EI+): *m*/*z* calcd for $C_{16}H_{15}O_4$: 271.0963, found $[M+H]^+$: 271.0965.

Analytical data matches previously reported characterisation.

71. 1-(6-Methoxynaphthalen-2-yl)-2-phenylethanone:[20]



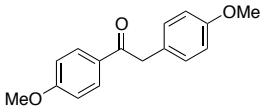
Yield 83%, 229 mg, white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (dd, *J* = 1.8, 0.8 Hz, 1H), 8.04 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.85 (dd, *J* = 9.0, 0.7 Hz, 1H), 7.78-7.74 (m, 1H), 7.38-7.30 (m, 4H), 7.30-7.21 (m, 1H), 7.20 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 4.39 (s, 2H), 3.95 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 160.0, 137.4, 135.0, 132.2, 131.3, 130.4, 129.6, 128.8, 127.9, 127.3, 127.0, 125.2, 119.9, 105.8, 55.6, 45.5.

Analytical data matches previously reported characterisation.

72. 1-(4-Methoxyphenyl)-2-(4-methoxyphenyl)ethanone:



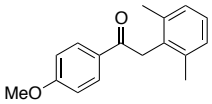
Yield 84%, 215 mg, white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03-7.96 (m, 2H), 7.21-7.15 (m, 2H), 6.96-6.90 (m, 2H), 6.89-6.83 (m, 2H), 4.17 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.6, 163.6, 158.5, 131.0, 130.5, 129.7, 127.0, 114.2, 113.9, 55.6, 55.3, 44.5.

HRMS (EI+): *m*/*z* calcd for $C_{16}H_{17}O_3$: 257.1172, found $[M+H]^+$: 257.1172

73. 2-(2,6-Dimethylphenyl)-1-(4-methoxyphenyl)ethan-1-one:[3]



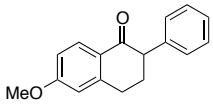
Yield 51%, 130 mg, white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.04 (m, 2H), 7.12-7.04 (m, 3H), 7.00-6.96 (m, 2H), 4.33 (s, 2H), 3.90 (s, 3H), 2.22 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 163.6, 137.0, 132.9, 130.4, 130.2, 128.0, 126.8, 113.9, 55.5, 39.3, 20.5.

Analytical data matches previously reported characterisation.

79. 6-Methoxy-2-phenyl-3,4-dihydronaphthalen-1(2H)-one:



Yield 82%, 1.18 g (5.7 mmol scale).

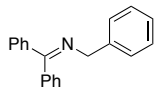
For characterisation, see entry **55**, **Chapter 2**.

7.5 Experimental data for Chapter 5

Synthesis and characterization of imines 22-50. [21]

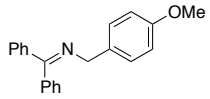
Benzophenone (3.6 g, 20 mmol), $NaHCO_3$ (8.4 g, 0.1 mol), the corresponding benzyl amine (21 mmol) and activated molecular sieves (4Å) were weighted in a round bottom flask under dry conditions. Then, dry toluene (40 mL) was added. The reaction was then stirred for 16 hours at 90°C. After this time, the mixture was filtered through celite. The desired imine was obtained pure, in quantitative yield, after recrystallization (AcOEt:*n*-hexane).

22 N-(Diphenylmethylene)-1-phenylmethanamine:



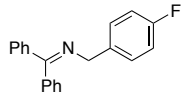
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.65 (m, 2H), 7.51-7.34 (m, 10H), 7.25-7.20 (m, 3H), 4.62 (m, 3H), 7.10-7.07 (m, 4H), 5.52 (s, 2H), 2.31 (s, 3H).

N-(Diphenylmethylene)-1-(4-methoxyphenyl)methanamine:



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.65 (m, 2H), 7.51-7.34 (m, 6H), 7.26-7.19 (m, 4H), 6.89 (m, 2H), 4.55 (s, 2H), 5.52 (s, 2H), 3.80 (s, 3H).

N-(Diphenylmethylene)-1-(4-fluorphenyl)methanamine:



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.68 (m, 2H), 7.51-7.28 (m, 8H), 7.23-7.19 (m, 2H), 7.05-6.99 (m, 2H), 4.58 (s, 2H).

General procedure for the arylation of imines.

Inside a glovebox, [Ni(COD)$_2$] (3.4 or 5.2 mg, 5.0 or 7.5 mol%, 0.0125 or 0.0188 mmol), IPr (10 or 15 mg, 2.0 equivalents with respect of Ni) the selected imine (0.5 mmol, 2.0 equivalents), KHMDS (100 mg, 0.5 mmol, 2 equivalents) were weighted in a screw cap vial equipped with a stirring bar. The aryl chloride (0.25 mmol, 1 equivalents) was added at this stage, if solid. The vial was sealed and carried out from the glovebox, where and the aryl chloride, if liquid, and the dry, degassed solvent (toluene, 1.5 ml) were added. The reaction was then stirred for 16 hours at 45°C. The reaction was then quenched adding some drops of water and filtered through Mg_2SO_4. After checking the NMR, the crude was absorbed on silica previously basified (stirring it overnight with 2% triethylamine in pentane) and purified by flash chromatography (typically with a pentane / diethyl ether = 95 / 5 eluent mixture) to afford the desired product quantitatively.

Procedure for the hydrolisys of 46 to 46'.

HCl 1N in diethyl ether (1 mL) was added to the solution of imine **3k** (39.7 mg, 0.1 mmol) in THF (1 mL) at 0°C. The solution was warmed to room temperature and stirred, monitoring by TLC until all the imine was consumed. The THF was evaporated under vacuum. Another 1 mL HCl (1N) was added and a white precipitate was observed. The white solid was filtered and washed with cold Et_2O (1.0 mL×3). After

drying under vacuum for 12 h, the hydrochloride salt was obtained as a white solid (25.4 mg, 99% yield).

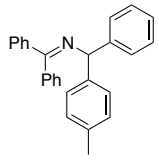
Procedure for the studies of the effect of the bases (Table 3).

Entries 1-3: Inside a glovebox, **22** (54 mg, 0.2 mmol, 1.0 equivalents) and the base (2.0 equivalents) were weighted in a screw cap vial equipped with a stirring bar. Outside the glovebox, toluene (0.6 mL) and benzyl chloride (0.25 μL, 2.4 mmol, 1.2 equivalents) were added, and the reaction was then stirred at 45 °C for 3 hours. The reaction was then quenched with 2 drops of water, filtered through $MgSO_4$ and dried under vacuum. The yield was then assessed *via* quantitative ^{1}H-NMR, using diethylmalonate as internal standard.

Entries 4-6: Inside a glovebox, **22** (54 mg, 0.2 mmol, 1.0 equivalents) and the base (0.5 equivalents) were weighted in a screw cap vial equipped with a stirring bar. Outside the glovebox, dry degassed toluene (0.6 mL) was added using a syringe through the septum, and the reaction was then stirred at 45 °C for 3 hours. The reaction was then quenched with 2 drops of water, filtered through $MgSO_4$, dried under vacuum and analyzed via ^{1}H-NMR.

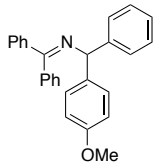
Characterization data.

27. *N*-(Diphenylmethylene)-1-phenyl-1-(*p*-tolyl)methanamine: [21]



From **22** and 4-chlorotoluene, 5% Ni loading. Yield 88%, 159 mg, yellow solid.
From **2'** and 4-chlorotoluene, 5% Ni loading. Yield 84%, 152 mg.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 2H), 7.45-7.41 (m, 3H), 7.38-7.27 (m, 7H), 7.22-7.18 (m, 3H), 7.10-7.07 (m, 4H), 5.52 (s, 2H), 2.31 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 141.9, 139.9, 136.7, 136.1, 130.0, 129.0, 128.7, 128.4, 128.4, 128.3, 127.9, 127.8, 127.5, 127.4, 126.6, 69.6, 21.1.
Analytical data matches previously reported characterisation.

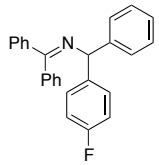
37. *N*-(Diphenylmethylene)-1-(4-methoxyphenyl)-1-phenylmethanamine: [21]



From **22** and 4-chloroanisole, 5% Ni loading. Yield 86%, 163 mg, white solid.
From **22-OMe** and chlorobenzene, 5% Ni loading Yield 86%, 163 mg.
From **22'** and 4-chloroanisole, 5% Ni loading, yield 83%, 157 mg.

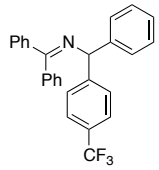
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J= 7.2 Hz, 2H), 7.45-7.25 (m, 10H), 7.22-7.18 (m, 3H), 7.11-7.08 (m, 2H), 7.10-7.07 (m, 4H), 6.83 (d, *J*=8.8 Hz, 2H), 5.53 (s, 1H), 3.78 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.57, 158.31, 145.11, 139.85, 137.15, 136.73, 129.98, 128.71, 128.58, 128.42, 128.37, 128.27, 127.96, 127.73, 127.44, 126.56, 113.70, 69.19, 55.20.
Analytical data matches previously reported characterisation.

38. *N*-(Diphenylmethylene)-1-(4-fluorophenyl)-1-phenylmethanamine:[21]



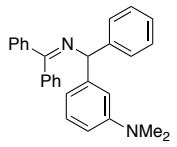
From **22** and 4-fluorochlorobenzene, 5% Ni loading. Yield 82%, 150 mg, yellow solid.
From **22-F** and chlorobenzene, 5% Ni loading. Yield 82%, 149 mg.
From **22'** and 4-fluorochlorobenzene, 5% Ni loading. Yield 82%, 149 mg
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (m, 2H), 7.47-7.44 (m, 3H), 7.40-7.30 (m, 2H), 7.30-7.26 (m, 6H), 7.24-7.18 (m, 1H), 7.10-7.06 (m, 2H), 7.00-6.94 (m, 2H), 5.55 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 162.0 (d, $^{1}J_{C\text{-}F}$= 243.0 Hz), 144.7, 140.6 (d, $^{4}J_{C\text{-}F}$= 3.0 Hz), 139.7, 136.6, 130.1, 129.0 (d, $^{3}J_{C\text{-}F}$= 7.8 Hz), 128.7, 128.5, 128.4, 128.4, 128.0, 127.6, 127.4, 126.8, 115.0 (d, $^{2}J_{C\text{-}F}$= 31.2 Hz), 69.3.
^{19}F NMR (376.8 MHz, $CDCl_3$): δ -116.4
Analytical data matches previously reported characterisation.

39. *N*-(Diphenylmethylene)-1-phenyl-1-(4-(trifluoromethyl)phenyl)methanamine:[21]



5% [Ni] loading. Yield 79%, 164 mg, brown solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (m, 2H), 7.55 (app. d, J= 8.4 Hz, 2H), 7.48-7.26 (m, 12H), 7.25-7.21 (m, 1H), 7.24-7.18 (m, 1H), 7.09-7.05 (m, 2H), 5.61 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 148.8, 144.0, 139.5, 136.5, 130.3, 129.0, 128.8, 128.7, 128.5, 128.0, 127.8, 127.6, 127.0, 125.3 (q, $J_{C\text{-}F}$= 3.4 Hz), 123.4 (q, $J_{C\text{-}F}$= 270.1 Hz), 69.5
^{19}F NMR (376.8 MHz, $CDCl_3$): δ -62.4
Analytical data matches previously reported characterisation.

40. 3-(((Diphenylmethylene)amino)(phenyl)methyl)-*N*,*N*-dimethylaniline:[22]



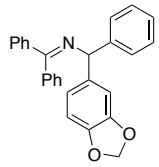
5% Ni loading. Yield 77%, 151 mg, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (m, 2H), 7.45-7.42 (m, 3H), 7.37-7.33 (m, 5H), 7.29-7.25 (m, 3H), 7.20-7.08 (m, 4H), 6.74 (m, 1H), 6.70 (m, 1H), 6.59 (ddd, *J*= 8.4 Hz, 2.8 Hz, 0.8 Hz, 1H),5.51 (s, 2H), 2.90 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5, 150.6, 145.6, 145.0, 139.9, 136.8, 129.9, 128.9, 128.72, 128.4, 128.3, 128.2, 127.9, 127.8, 127.5, 126.5, 116.2, 112.0, 111.0, 70.1, 40.7.

Analytical data matches previously reported characterisation.

41. 1-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(diphenylmethylene)-1-phenylmethanamine:



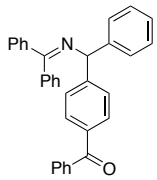
5% Ni loading. Yield 86%, 169 mg, white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (m, 2H), 7.48-7.28 (m, 11H), 7.26-7.20 (m, 1H), 7.13 (d, *J*= 2 Hz, 1H), 7.11 (m, 1H), 6.95 (d, *J*= 1,6 Hz, 1H), 6.78 (dd, J^1=8.4 Hz, J^2=1.6 Hz, 1H), 6.74 (d, *J*= 8 Hz, 1H), 5.92 (s, 2H), 5.51 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 147.6, 146.2, 144.9, 139.7, 138.9, 136.6, 130.1, 128.71, 128.5, 128.4, 128.3, 128.0, 127.7, 127.3, 126.7, 120.4, 108.3, 107.9, 100.8, 69.4.

HRMS (EI+): *m*/*z* calcd for $C_{27}H_{21}NO_2$: 390.1489, found $[M+H]^+$: 390.1481

42. 4-(((Diphenylmethylene)amino)(phenyl)methyl)phenyl)(phenyl)methanone:



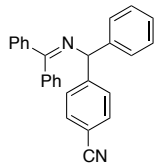
5% Ni loading. Yield 89%, 201 mg, yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85-7.80 (m, 6H), 7.59 (t, *J*= 7.5 Hz, 1H), 7.53-7.47 (m, 7H), 7.45-7.39 (m, 5H), 7.35 (t, *J*= 7.5 Hz, 2H), 7.29-7.24 (m, 1H), 7.14-7.11 (m, 2H), 5.69 (s, 2H), 2.31 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 196.4, 167.6, 149.6, 144.1, 139.5, 137.7, 132.2, 130.3, 130.25, 130.0, 128.7, 128.6, 128.4, 128.2, 128.0, 127.6, 127.5, 127.4, 127.0, 69.7.

HRMS (EI+): *m*/*z* calcd for $C_{33}H_{25}NO$: 450.1852, found $[M+H]^+$: 450.1548

43. 4-(((Diphenylmethylene)amino)(phenyl)methyl)benzonitrile:[21]



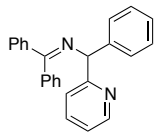
5% Ni loading. Yield 80%, 149 mg, off white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.73 (m, 2H), 7.57 (d, J= 8.4 Hz, 2H), 7.47-7.36 (m, 15H), 7.06-7.3 (m, 2H), 5.57 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 150.2, 143.6, 139.3, 136.3, 132.2, 130.4, 128.7, 128.61, 128.6, 128.2, 128.1, 127.5, 127.5, 127.2, 119.0, 110.5, 69.5.

Analytical data matches previously reported characterisation.

44. *N*-(Diphenylmethylene)-1-phenyl-1-(pyridin-2-yl):



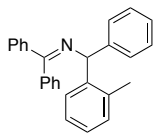
7.5% Ni loading. Yield 89%, 155 mg, brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (d, J= 4.5 Hz, 1H), 7.83-7.77 (m, 3H), 7.67 (dt, *J*= 7.5, 1.5 Hz, 1H), 7.42-7.35 (m, 8H), 7.28 (t, *J*= 7.5 Hz, 2H), 7.22-7.18 (m, 1H), 7.12-7.09 (ddd, *J*= 7.5 Hz, 4 Hz, 1 Hz, 1H), 7.07-7.04 (m, 2H), 5.77 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 163.9, 148.9, 144.0, 139.8, 136.7, 136.3, 130.2, 128.8, 128.6, 128.4, 128.4, 128.0, 127.7, 127.5, 126.8, 122.0, 121.8, 71.9.

HRMS (EI+): *m*/*z* calcd for $C_{25}H_{20}N_2$: 347.1543, found $[M+H]^+$: 347.1539

45. *N*-(Diphenylmethylene)-1-phenyl-1-(*o*-tolyl)methanamine:[21]



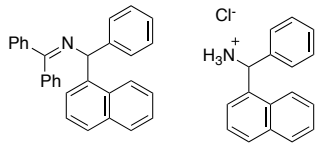
7.5% Ni loading. Yield 75%, 135 mg, brown solid .

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.74 (m, 2H), 7.71 (d, J= 7.6 Hz, 1H), 7.46-7.18 (m, 13H), 7.09-7.06 (m, 3H), 5.76 (s, 1H), 1.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 144.0, 142.7, 139.8, 137.0, 135.3, 130.3, 130.0, 128.7, 128.5, 128.4, 128.2, 128.0, 127.6, 126.6, 126.5, 126.1, 66.7, 19.5.

Analytical data matches previously reported characterisation.

46. Naphthalen-1-yl(phenyl)methanaminium chloride: [21]



7.5% Ni loading. Yield 61%, 71 mg (after hydrolisis), white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.94 (m, 3H), 7.72-7.63 (m, 2H), 7.56-7.37 (m, 7H), 6.44 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 135.6, 131.4, 130.6, 130.3, 130.2, 130.1, 129.1, 128.5, 128.0, 127.4, 126.2, 124.4, 124.2, 56.1.

Analytical data matches previously reported characterisation.

7.6 Experimental details for Chapter 6

Typical procedure for the arylation of ketones with haloindoles.

A vial containing a stirring bar was charged with (Pd(D*t*BPF)Cl_2) **43** (2.0 mol%, 2.6 mg). haloindole (0.2 mmol, 1.0 equivalents) was added. The vial was then closed with a septum cap and the liquid ketone (0.8 mmol, 4.0 equivalents) was added. The vial was purged three times with Ar/vacuum cycles. A stock solution of NaOH in water was prepared (160 mg/mL, 4.0 M). Under an Ar atmosphere, dioxane (0.2 mL), the ketone and and the aqueous NaOH solution (4.0 equivalents, 0.2 mL) were added through the septum using a syringe. Finally, the vial was stirred at 60°C for 16 h. The solution was cooled to room temperature, then 0.5 mL water and 0.5 mL of ethyl acetate were added and mixed. The aqueous phase was then extracted with ethyl acetate (4 x 1 mL) and the organic phase was filtered through a short pad of $MgSO_4$. The product was then purified via column chromatography (typically hexane : acetate = 9 : 1).

Typical procedure for the arylation of ketones with other haloarenes.

A vial containing a stirring bar was charged with (Pd(D*t*BPF)Cl_2) **43** (2.0 mol%, 2.6 mg). All the solid coupling partners were added at this stage: solid haloarenes (0.2 mmol, 1.0 equivalents) and/or solid ketones (0.4 mmol, 2.0 equivalents). The vial was then closed with a septum cap and purged three times with Ar/vacuum cycles. A stock solution of NaOH in water was prepared (100 mg/mL). Under an Ar atmosphere, dioxane (0.2 mL), the liquid ketone and/or the liquid haloarene, and the aqueous NaOH solution (2.5 equivalents, 0.2 mL) were added through the septum using a syringe. Finally, the vial was stirred at 60°C for 16 h. The solution was cooled to room temperature, then 0.5 mL water and 0.5 mL of ethyl acetate were added and mixed. The aqueous phase was then extracted with ethyl acetate (4 x 1 mL) and the organic phase was filtered through a short pad of $MgSO_4$. The product was then purified via column chromatography (typically hexane : acetate = 9 : 1).

Synthesis of Prochlorperazine derivative 75.

Proclorperazine dimaleate (0.2 mmol, 121.2 mg) was suspended in 2 mL of ethyl acetate. To this suspension, 2 mL of 1.0 M aqueous Na_2CO_3 was added. After the organic phase became clear, the aqueous phase was separated and extracted again with ethyl acetate (4 x 2 mL). The combined organic extract was evaporated and the remaining oil was dissolved in dioxane and transferred to a vial. After evaporation of the solvent, (Pd(DTBPF)Cl_2) (5 mol%, 6.5 mg) was weighted in the vial. The vial was then closed with a septum cap and purged three times with Ar/vacuum cycles. A stock solution of NaOH in water was prepared (160 mg/mL). Under an Ar atmosphere, dioxane (0.2 mL), propiophenone (2.0 equivalents, 50 uL), and the aqueous NaOH solution (4.0 equivalents, 0.2 mL) were added through the septum using a syringe. Finally, the vial was stirred at 60°C during 16 h. The solution was cooled to r.t., then 0.5 mL water and 0.5 mL of ethyl acetate were added and mixed. The aqueous phase was then extracted with ethyl acetate (4 x 1 mL) and the organic phase was filtered through a short pad of $MgSO_4$ and evaporated. The resultant crude oil was suspended in ethyl ether (5 mL) and 0.1 M HCl (5 mL). The aqueous phase wash washed with ethyl ether (3 x 5 mL) and then the pH was adjusted to *ca*. 11 using a saturated solution of Na_2CO_3. This basic aqueous solution was then extracted with ethyl acetate (6 x 5mL), dried over $MgSO_4$ and evaporated. The mixture was then purified by flash chromatography (97:3 DCM/MeOH) over pre-treated, basified silica (2% triethylamine in DCM, overnight), affording 248 mg (86%) of the product **75** as a pale, yellow oil.

Synthesis of N-Boc protected halotryptophans 78, 81, 83.[23]

A suspension of S-7-Br-tryptophan (100 mg, 0.35 mmol, 1.0 eq) and di-*t*-butyl dicarbonate (92 mg, 0.42 mmol, 1.2 eq) in 1,4-dioxane-water (1:1, 3.0 mL) was cooled to 0 °C. Aqueous KOH (1 M, 0.45 mL, 0.45 mmol, 1.25 eq) was added dropwise. The mixture was stirred overnight while warming to room temperature. The reaction was diluted with water (10 mL) and extracted with diethyl ether (2 x 10 mL). The aqueous layer was cooled in an ice-bath and the pH was adjusted to 2 using 1 M HCl. The resulting white suspension was extracted using ethyl acetate (5 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give *S*-N-Boc-7-Br-tryptophan **83** (120 mg, 89%) as a white, waxy solid that was used without further purification. Analogous procedures were used for the preparation of *S*-N-Boc-5-Br-tryptophan and 6-Cl-*S*-tryptophan.

Coupling of N-Boc protected halotryptophans.

S-N-Boc-5-Br-tryptophan (0.05 mmol, 19.2 mg) and [Pd(D*t*BPF)Cl_2] **43** (10 mol%, 3.6 mg) were weighted in a screw-cap vial equipped with a stirring bar. The vial was then purged with 3 cycles of vacuum/Ar. Dioxane (0.1 mL; previously filtered on basic alumina), propiophenone (5.0 equivalents, 30 μL) and an aqueous solution of NaOH

(0.1 mL of a 2M solution, 4.0 equivalents) were added in this order, and the reaction was stirred at 60°C for 16 h. After this time, the reaction was cooled to r.t., 2 mL of water was added and the dioxane was evaporated at the rotavapor. The resulting aqueous solution was extracted with ethyl ether (3 x 3 mL). The pH of the solution was then adjusted to *ca*. 2, and the resulting suspension was extracted with ethyl acetate (6 x 3 mL). The ethyl acetate phases were combined and dried on Na_2SO_4, then filtered and concentrated under vacuum. The crude mixture was then purified either by column chromatography (DCM/Ethyl acetate/formic acid = 9:1:0.1) or by automated column chromatography on C18-functionalised reverse phase silica using a gradient of water and methanol (5-95%) to afford product **79** as a white solid. The same protocol was applied for the synthesis of compounds **81** and **83**.

Assessment of the enantiopurity of 83.

Boc-deprotection of 83 using TFA

6h (10 mg, 0.023 mmol) was dissolved in CH_2Cl_2 (1 mL) and transferred to a microwave vial. TFA (50 μL, ca. 2 mmol) was added and reaction vial was sealed with an aluminium crimp cap. Reaction mixture was heated in a microwave reactor at 60°C for 40 min. After cooling, solvent was evaporated under reduced pressure.

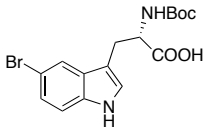
Enantiopurity analysis of tryptophan derivatives by UPLC after derivatisation with Marfey's reagent.[24]

The enantiopurity of Boc-deprotected **83** was analysed using Marfey's Reagent (1-fluoro-2,4-dinitrophenyl-5-L-alanine amide, FDAA).

A stock solution of 10.0 mM FDAA in acetone was prepared by dissolving 2.7 mg FDAA in 1 ml acetone. The sample was dissolved in 1 M sodium hydrogen carbonate (0.5 mg/mL). FDAA (50 μl) stock solution were added to 100 μl of sample solution, and the mixture incubated at 40 °C for 1h. The reaction was quenched with 100 μl of 1 M hydrochloric acid. The reaction mixture was diluted (10 ml in 190 ml water) and centrifuged (13,000 rpm, 5 min). Clear supernatant was analysed by UPLC: the analysis was performed on Waters Acquity UPLC BEH C18 (1.7um 2.1 x 50 mm) column eluting with 0.1% TFA in water (solvent A) and acetonitrile (solvent B). Following gradient was used: 0-0.2 min (20% B), 0.2-4.0 min (20% to 70% B), 4.0-4.2 (70% to 90% B), 4.2-5.2 min (90% B), 5.2-5.5 (90% to 20%B), 5.5-6.0 (20% B). The flow rate was set to 600 μl min^{-1} and the column temperature was maintained at 50°C. Detection was by UV (PDA 200-400nm, UV 340 nm). A mixture of S-tryptophan to D-tryptophan was used as a standard to confirm the separation of enantimers. The FDAA derivative of Boc-deprotected **6h** revealed only peak, indicating presence of single enantiomer. The stereocenter in the α-position of the ketone carbonyl moiety did not affect the analysis.

Characterisation data.

78. *S*-N-Boc-5-Br-tryptophan:[25]



Yield 87%, 123 mg.

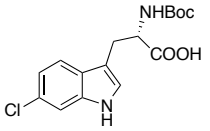
^{1}H NMR (400MHz, CD_3OD) : δ 7.71 (d, *J* = 1.6 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.12 (s, 1H), 4.40 (dd, *J* = 7.4, 5.0 Hz, 1H), 3.27 (dd, *J* = 14.6, 4.8 Hz, 1H), 3.09 (dd, *J* = 14.6, 7.7 Hz, 1H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, CD_3OD): δ 175.5, 157.7, 136.6, 130.8, 126.0, 125.0, 122.0, 113.9, 113.0, 111.1, 80.6, 56.0, 29.4, 28.7.

$[\alpha]^{20}_D$ = -1.4 (c= 0.5, MeOH)

Analytical data matches previously reported characterisation.

80. *S*-N-Boc-6-Cl-tryptophan:



Yield 88%, 119 mg,.

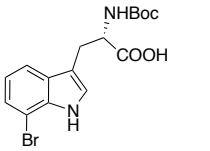
^{1}H NMR (400MHz, CD_3OD) : δ 7.52 (d, *J* = 8.5 Hz, 1H), 7.33 (s, 1H), 7.10 (s, 1H), 6.98 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.39 (dd, *J* = 7.7, 5.2 Hz, 1H), 3.31-3.24 (m, 1H, partly covered by the solvent signal), 3.09 (dd, *J* = 14.6, 7.9 Hz, 1H), 1.38 (s, 9H).

^{13}C NMR (101 MHz, CD_3OD) : δ 175.7, 157.8, 138.3, 128.2, 127.6, 125.4, 120.5, 120.2, 112.0, 111.6, 80.5, 55.8, 28.7, 28.6.

$[\alpha]^{20}_D$ = +5.4 (c= 0.5, MeOH)

HRMS (EI+): *m*/*z* calcd for $C_{16}H_{20}{}^{35}ClN_2O_4$: 339.1111, found $[M+H]^+$: 339.1113

82. *S*-N-Boc-7-Br-tryptophan:[26]



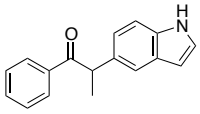
Yield 91%, 127 mg.

^{1}H NMR (300MHz, CD_3OD) : δ 10.55 (bs, 1H), 7.56 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.17 (s, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 4.43 (dd, *J* = 7.7, 5.2 Hz, 1H), 3.31 (dd, *J* = 14.9, 4.5 Hz, 2H), 3.11 (dd, *J* = 14.6, 7.8 Hz, 1H), 1.37 (s, 9H).

^{13}C NMR (101 MHz, CD_3OD): δ 174.3, 156.3, 129.1, 124.3, 124.2, 123.5, 119.6, 117.5, 111.2, 111.2, 104.1, 79.2, 54.4, 27.4, 27.3.

$[\alpha]^{20}_D$ = +15.2 (c= 0.5, MeOH)

57. 2-(1*H*-Indol-5-yl)-1-phenylpropan-1-one:



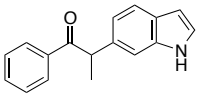
Yield 84%, 126 mg. X=Br, brown solid.

^{1}H NMR (400MHz, $CDCl_3$) : δ 8.19 (bs, 1H), 8.04-7.99 (m, 2H), 7.56 (d, *J*=1.2 Hz, 1H), 7.46-7.40 (m, 1H), 7.38-7.29 (m, 3H), 7.17-7.14 (m, 1H), 7.13 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.49 (ddd, *J* = 3.0, 2.0, 0.9 Hz, 1H), 4.79 (q, *J* = 6.8 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 201.0, 136.7, 134.8, 132.9, 132.5, 128.9, 128.3, 124.7, 121.9, 119.7, 111.6, 102.47, 48.0, 20.0. One aromatic carbon was not detected.

HRMS (EI+): *m*/*z* calcd for $C_{17}H_{17}NO$: 250.1226, found $[M+H]^+$: 250.1224.

58. 2-(1*H*-Indol-6-yl)-1-phenylpropan-1-one:



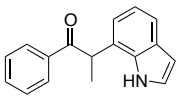
Yield 82%, 123 mg. X=Br, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.24 (bs, 1H), 8.00 (dt, *J* = 8.5, 1.7 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.48-7.40 (m, 1H), 7.35 (ddt, *J* = 8.2, 6.8, 1.2 Hz, 2H), 7.27 (s, 1H), 7.13 (m, 1H), 7.10 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.49 (ddd, *J* = 3.0, 2.0, 0.9 Hz, 2H), 4.79 (q, *J* = 6.8 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 200.8, 136.6, 136.2, 135.4, 132.6, 128.8, 128.4, 126.7, 124.4, 121.2, 120.3, 109.8, 102.4, 77.0, 48.1, 19.9.

HRMS (EI+): *m*/*z* calcd for $C_{17}H_{17}NO$: 250.1226, found $[M+H]^+$: 250.1226.

59. 2-(1*H*-Indol-6-yl)-1-phenylpropan-1-one:



Yield 90%, 135 mg. X=Br, brown solid.

Yield 85%, 128 mg. X=I.

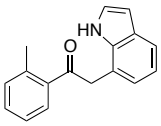
Yield 81%, 122 mg. X=Cl (Pd 5 mol%).

^{1}H NMR (400MHz, $CDCl_3$) : δ 9.13 (s, 1H), 8.10 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.23 (dd, *J* = 5.0, 1.9 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.54 (ddd, *J* = 3.0, 2.0, 0.9 Hz, 1H), 5.04 (q, *J* = 7.0 Hz, 1H), 1.72 (d, *J* = 7.0 Hz, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) : δ 201.8, 136.3, 133.9, 133.3, 129.1, 128.9, 128.5, 124.7, 122.9, 122.5, 120.2, 120.1, 102.3, 47.2, 16.8.

HRMS (EI+): *m*/*z* calcd for $C_{17}H_{17}NO$: 250.1226, found $[M+H]^+$: 250.1224.

60. 2-(1*H*-Indol-7-yl)-1-(*o*-tolyl)-ethan-1-one:



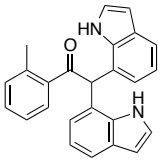
Yield 69%, 103 mg. X=Br, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.00 – 7.87 (m, 1H), 7.56 (dd, *J* = 6.6, 2.1 Hz, 1H), 7.35 (td, *J* = 7.5, 1.2 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.12 – 6.97 (m, 2H), 6.59 – 6.51 (m, 1H), 4.43 (s, 2H), 2.40 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9, 139.2, 136.9, 135.6, 132.1, 131.8, 129.5, 128.4, 125.64, 124.8, 123.3, 120.0, 117.0, 102.6, 46.7, 21.4. One aromatic carbon was not detected.

HRMS (EI+): *m*/*z* calcd for $C_{17}H_{17}NO$: 250.1226, found $[M+H]^+$: 250.1225.

60′. 2,2-di(1H-Indol-7-yl)-1-(*o*-tolyl)-ethan-1-one:



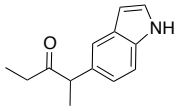
20 mg, 9% yield of this product were isolated from the reaction for **60**, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 2H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.40 (td, *J* = 7.5, 1.2 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.01 (t, *J* = 2.8 Hz, 2H), 6.48 (dd, *J* = 3.1, 2.1 Hz, 2H), 6.42 (s, 1H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.2, 139.1, 138.3, 134.8, 132.1, 131.9, 129.1, 128.7, 125.87, 124.8, 122.5, 120.8, 120.3, 120.0, 102.4, 58.4, 21.0.

HRMS (EI+): *m*/*z* calcd for $C_{25}H_{21}N_2O$: 365.1648, found $[M+H]^+$: 365.1651.

61. 2-(1H-Indol-5-yl)-pentan-3-one:



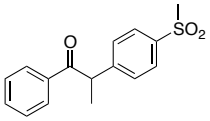
Yield 45%, 54 mg. X=Br, brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.52 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.53 (s, 1H), 3.88 (q, *J* = 6.9 Hz, 1H), 2.70 – 2.14 (m, 2H), 1.48 (d, *J* = 8.1 Hz, 3H), 0.98 (t, *J* = 7.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 212.9, 134.9, 132.2, 128.2, 124.9, 121.7, 119.7, 111.5, 102.2, 52.7, 34.0, 17.9, 8.0.

HRMS (EI+): *m*/*z* calcd for $C_{13}H_{16}NO$: 202.1226, found $[M+H]^+$: 202.1225.

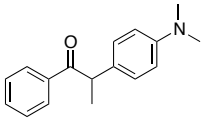
62. 2-(4-(Methylsulfonyl)phenyl)-1-phenylpropan-1-one:



Yield 92%, 159 mg. X=Cl.

For characterisation, see entry **46**, **Chapter 2**.

63. 2-(4-(Dimethylamino)phenyl)-1-phenylpropan-1-one:[27]



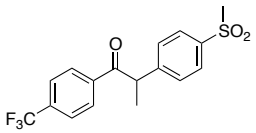
Yield 92%, 140 mg. X=Br, pale yellow solid.

H NMR (400MHz, $CDCl_3$) : δ 7.97 (m, 2H), 7.46 (m, 1H), 7.37 (m, 2H), 7.16 (m, 2H), 6.67 (m, 2H), 4.60 (q, *J* = 6.8 Hz, 1H), 2.90 (s, 6H), 1.51 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 149.3, 136.7, 132.5, 129.1, 128.7, 128.4, 128.4, 113.04, 46.8, 19.4.

Analytical data matches previously reported characterisation.

64. 2-(4-(Methylsulfonyl)phenyl)-1-(4-(trifluoromethyl)phenyl)propan-1-one:



Yield 88%, 188 mg. X=Cl, brown solid.

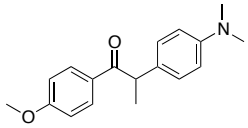
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 4.79 (q, *J* = 6.9 Hz, 1H), 2.99 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 146.7, 139.3, 138.5, 134.7, 134.4, 134.2 (q, *J* = 32.8 Hz), 134.0, 133.7, 128.9, 128.7, 128.0, 127.4, 127.4, 127.3, 127.3, 125.6, 125.6 (d, *J* = 3.5 Hz), 125.6, 124.6, 123.3 (q, *J* = 272.8 Hz), 121.9, 119.2, 119.2, 47.7, 44.1, 19.1.

^{19}F NMR (377 MHz, $CDCl_3$) δ -63.18.

HRMS (EI+): (*m*/z): $[M+H]^+$ calcd for $C_{17}H_{16}F_3O_3S$, 357.0775; found, 357.0775

65. 2-(4-(Dimethylamino)phenyl)-1-(4-methoxyphenyl)propan-1-one:

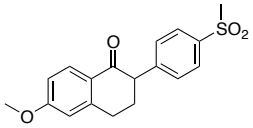


Yield 95%, 162 mg. X=Br, yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.92 (m, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 4.57 (q, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 2.89 (s, 6H), 1.51 (s, 3H).

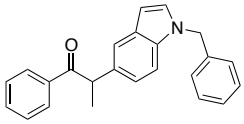
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 162.9, 149.3, 130.9, 129.5, 129.5, 128.2, 113.4, 112.87, 55.2, 46.4, 40.4, 19.4.
HRMS (EI+): *m*/*z* calcd for $C_{18}H_{22}NO_2$: 284.1645, found $[M+H]^+$: 284.1641.

66. 6-methoxy-2-(4-(Methylsulfonyl)phenyl)-3,4-dihydronaphthalen-1(2H)-one:[28]



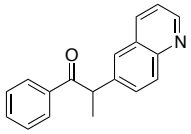
Yield 63%, 124 mg. X=Cl, brown solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 3.88 (s, 3H), 3.87-3.83 (m, 1H), 3.19-3.08 (m, 1H), 3.05 (s, 3H) 3.04-2.96 (m, 1H), 2.41 (td, *J* = 9.2, 7.9, 4.4 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 163.9, 146.6, 146.3, 138.9, 130.3, 129.6, 127.5, 125.95, 113.5, 112.6, 77.3, 55.5, 54.2, 44.6, 31.2, 29.3.
Analytical data matches previously reported characterisation.

67. 2-(1-Benzyl-1H-indol-5-yl)-1-phenylpropan-1-one:



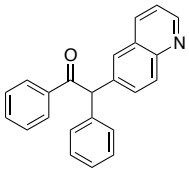
Yield 83%, 177 mg. X=Br, brown solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.47 – 7.39 (m, 1H), 7.38 – 7.33 (m, 2H), 7.32 – 7.26 (m, 3H), 7.26 – 7.20 (m, 1H), 7.15 – 7.05 (m, 4H), 6.49 (dd, *J* = 3.1, 0.7 Hz, 1H), 5.26 (s, 2H), 4.78 (q, *J* = 6.8 Hz, 1H), 1.58 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8, 137.3, 136.7, 135.4, 132.6, 132.5, 129.1, 128.8, 128.72, 128.7, 128.3, 127.6, 126.9, 121.7, 119.9, 110.2, 101.5, 50.1, 47.9, 19.9.
HRMS (EI+): *m*/*z* calcd for $C_{24}H_{22}NO$: 340.1696, found $[M+H]^+$: 340.1695.

68. 1-Phenyl-2-(quinolin-6-yl)propan-1-one:



Yield 83%, 130 mg. X=Cl, colourless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.8 Hz, 1H), 8.13 – 7.99 (m, 2H), 8.01 – 7.94 (m, 2H), 7.69 (m, 2H), 7.51 – 7.42 (m, 1H), 7.41 – 7.31 (m, 3H), 4.89 (q, *J* = 6.9 Hz, 1H), 1.62 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 150.2, 147.2, 139.8, 136.2, 135.9, 133.0, 130.1, 129.76, 128.7, 128.5, 128.4, 126.1, 121.3, 47.6, 19.5.
HRMS (EI+): *m*/*z* calcd for $C_{18}H_{16}NO$: 262.1226, found $[M+H]^+$: 262.1226.

69. 1,2-Diphenyl-2-(quinolin-6-yl)ethan-1-one:[29]



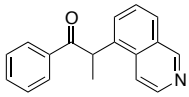
Yield 65%, 126 mg. X=Cl, brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.12 – 8.00 (m, 4H), 7.71 – 7.64 (m, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.37 – 7.32 (m, 5H), 7.28 (dd, *J* = 10.3, 6.0 Hz, 1H), 6.25 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 150.3, 147.3, 138.4, 137.6, 136.5, 136.0, 135.1, 133.19, 131.0, 129.7, 129.1, 128.9, 128.9, 128.6, 128.1, 127.5, 127.4, 126.4, 121.8, 121.2, 59.1.

Analytical data matches previously reported characterisation.

70. 1-Phenyl-2-(quinolin-5-yl)propan-1-one:



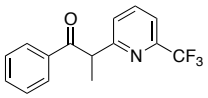
Yield 95%, 149 mg. X=Cl, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 0.7 Hz, 1H), 8.65 (d, *J* = 6.1 Hz, 1H), 7.97 (d, *J* = 6.4 Hz, 1H), 7.90-7.81 (m, 3H), 7.55-7.39 (m, 3H), 7.36-7.26 (m, 2H), 5.33 (q, *J* = 6.8 Hz, 1H), 1.64 (d, *J* = 6.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 153.7, 143.9, 137.2, 136.0, 133.4, 133.0, 129.3, 129.2, 128.6, 128.5, 127.2, 127.1, 115.6, 43.0, 18.5.

HRMS (EI+): *m*/*z* calcd for $C_{18}H_{16}NO$: 262.1226, found $[M+H]^+$: 262.1225.

71. 1-Phenyl-2-(6-(trifluoromethyl)176yridine-2-yl)propan-1-one:



Yield 74%, 125 mg. X=Cl, yellow solid.

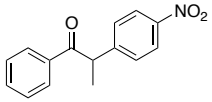
^{1}H NMR (400 MHz, CDCl3) δ 8.06 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.55 – 7.36 (m, 5H), 5.08 (q, *J* = 7.0 Hz, 1H), 1.62 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 161.6, 138.1, 136.0, 133.3, 129.0, 128.6, 124.7, 118.58 (q, *J*= 2.7 Hz), 50.4, 18.0. Trifluoromethyl carbon was not detected.j

^{19}F NMR (377 MHz, $CDCl_3$) δ -68.04.

HRMS (EI+): *m*/*z* calcd for $C_{15}H_{13}F_3NO$: 280.0939, found $[M+H]^+$: 280.0944.

72. 2-(4-Nitrophenyl)-1-phenylpropan-1-one:[30]



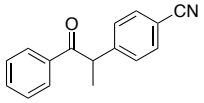
Yield 58%, 89 mg. X=Cl, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 2H), 7.93 (dt, *J* = 8.5, 1.6 Hz, 2H), 7.57 – 7.45 (m, 3H), 7.41 (t, *J* = 7.7 Hz, 2H), 4.84 (q, *J* = 6.9 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 148.6, 146.9, 135.8, 133.3, 128.7, 124.1, 47.3, 46.6, 44.5, 21.2, 20.3, 19.3, 19.0.

Analytical data matches previously reported characterisation.

73. 4-(1-Oxo-1-phenylpropan-2-yl)benzonitrile:[31]



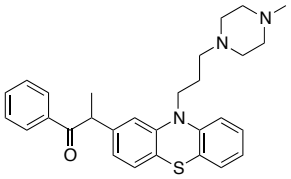
Yield 19%, 27 mg. X=Cl, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 1H), 7.62 – 7.56 (m, 1H), 7.56 – 7.50 (m, 0H), 7.45 – 7.38 (m, 2H), 4.77 (q, *J* = 6.9 Hz, 0H), 1.55 (d, *J* = 6.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 146.6, 135.9, 133.3, 132.7, 128.7, 128.6, 118.6, 110.93, 47.6, 19.3.

Analytical data matches previously reported characterisation.

75. 2-(10-(3-(4-Methylpiperazin-1-yl)propyl)-10*H*-phenothiazin-2-yl)-1-phenylpropan-1-one:



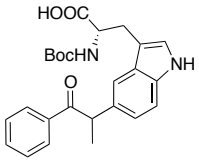
Yield 86%, 248 mg. X=Cl, brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.90 (m, 2H), 7.50 -7.44 (m, 1H), 7.40-7.34 (m, 2H), 7.14-7.06 (m, 2H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.90-6.83 (m, 3H), 6.72 (d, *J* = 1.6 Hz, 1H), 4.61 (q, *J* = 6.8 Hz, 2H), 2.58-2.15 (m, 13 H), 3.86 (t, *J* = 6.9 Hz, 2H), 1.85 (p, *J* = 7.0 Hz, 1H), 1.50 (d, *J* = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 145.7, 145.0, 140.7, 136.3, 132.9, 128.7, 128.5, 127.71, 127.3, 127.2, 124.9, 123.7, 122.4, 122.0, 115.6, 114.5, 55.4, 55.1, 53.1, 47.6, 46.0, 45.2, 24.2, 19.5.

HRMS (EI+): *m*/*z* calcd for $C_{29}H_{34}N_3OS$: 472.2417, found $[M+H]^+$: 472.2408.

79. (*S*)-2-[(*t*-Butoxycarbonyl)amino]-3-(5-(1-oxo-1-phenylpropan-2-yl)-1*H*-indol-3-yl)propanoic acid:



Yield 87%, 56 mg. X=Br, brown solid.

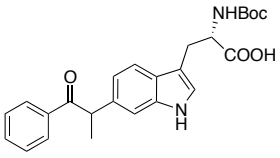
^{1}H NMR (400 MHz, CD_3OD) δ 10.28 (s, 1H), 8.00 (d, *J* = 7.4 Hz, 2H), 7.55-7.49 (m, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.06 (s, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 4.86-4.83 (m, partly covered by the signal of water, 1H), 4.41 (td, *J* = 8.0, 5.2 Hz, 1H), 3.26 (dd, *J* = 14.5, 5.4 Hz, 1H), 3.10 (dd, *J* = 15.4, 7.3 Hz, 1H), 1.53 (d, *J* = 6.7 Hz, 3H), 1.39 (d, *J* = 1.9 Hz, 9H).

^{13}C NMR (101 MHz, CD_3OD) 203.2, 176.0, 157.8, 138.1, 133.7, 133.3, 129.9, 129.4, 129.4, 125.2, 122.2, 118.7, 112.8, 111.1, 80.5, 55.9, 49.3, 48.4, 28.7, 23.7, 20.3. One aromatic carbon was not detected.

$[\alpha]^{20}_D$ = -30.2 (c= 0.5, MeOH)

HRMS (EI+): *m*/*z* calcd for $C_{25}H_{29}N_2O_5$: 437.2071, found $[M+H]^+$: 437.2071.

81. (*S*)-2-[(*t*-Butoxycarbonyl)amino]-3-(6-(1-oxo-1-phenylpropan-2-yl)-1*H*-indol-3-yl)propanoic acid:



Yield 70%, 45 mg. X=Cl, brown solid.

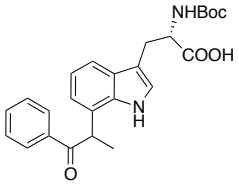
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.55-7.41 (m, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.22 (s, 1H), 7.03 (s, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 4.86-4.83 (m, partly covered by the signal of water, 1H), 4.41-4.32 (m, 1H), 3.29-3.20 (m, 1H), 3.07 (dd, *J* = 14.6, 7.9 Hz, 1H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.32 (d, *J* = 4.3 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0, 176.0, 157.7, 138.4, 138.1, 136.1, 133.7, 129.9, 129.44, 128.0, 124.8, 120.0, 119.9, 111.3, 111.1, 80.4, 56.0, 49.3, 28.7, 28.6, 20.1.

$[\alpha]^{20}_D$ = -2.2 (c= 0.5, MeOH)

HRMS (EI+): *m*/*z* calcd for $C_{25}H_{29}N_2O_5$: 437.2071, found $[M+H]^+$: 437.2071.

83. (*S*)-2-[(*t*-Butoxycarbonyl)amino]-3-(6-(1-oxo-1-phenylpropan-2-yl)-1*H*-indol-3-yl)propanoic acid:



Yield 94%, 60 mg. X=Br, yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.44 (dd, *J* = 7.5, 5.1 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.19 (s, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.3 Hz, 1H), 5.15 (q, *J* = 6.7 Hz, 1H), 4.47-4.34 (m, 1H), 3.29-3.28 (m, partly covered by the signal of deuterated methanol, 1H), 3.11 (dd, *J* = 14.7, 8.0 Hz, 1H), 1.53 (dd, *J* = 6.7, 1.3 Hz, 3H), 1.36 (d, *J* = 6.5 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 175.8, 157.8, 137.8, 134.0, 130.0, 129.5, 129.5, 125.8, 125.0, 124.8, 121.0, 120.5, 118.5, 112.2, 80.5, 55.9, 49.3, 44.7, 28.8, 28.7, 18.2. One aromatic carbon was not detected.

$[\alpha]^{20}_D$ = +23.4 (c= 0.5, MeOH)

HRMS (EI+): *m*/*z* calcd for $C_{25}H_{29}N_2O_5$: 437.2071, found $[M+H]^+$: 437.2071.

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Appendix: scientific contributions

Publications

"Computational studies on the mechanism of the Ni-catalysed carboxylation of boronate". M. Delarmolina, E. Marelli, S. P. Nolan, M. Buehl, *manuscript in preparation*.

"Living GenoChemetics: Hyphenating Synthetic Biology and Synthetic Chemistry in vivo". S. V. Sharma, X. Tong, C. Pubill-Ulldemolins, C. Cartmell, E. J. A. Bogosyan, E. J. Rackham, E. Marelli, R. B. Hamed, & R. J. M. Goss, *Nature Comm.*, *manuscript accepted*.

"Mild, Aqueous α-Arylation of Ketones: Towards New Diversification Tools for Halogenated Metabolites and Drug Molecules". E. Marelli, Y. Renault, S. V Sharma, S. P. Nolan, R. J. M. Goss, *Chem. – Eur. J.* **2017**, *23*, 3832–3836.

"α-Arylation of Imines Leading to N-Unprotected Indoles and Azaindoles". E. Marelli, M. Corpet, Y. Minenkov, R. M. Neyyappadath, A. Bismuto, G. Buccolini, M. Curcio, L. Cavallo, S. P. Nolan, *ACS Catal.* **2016**, *6*, 2930–2938.

"Arylation of Amines in Alkane Solvents by using Well-Defined Palladium–N-Heterocyclic Carbene Complexes". E. Marelli, A. Chartoire, G. Le Duc, S. P. Nolan, *ChemCatChem* **2015**, *7*, 4021–4024.

"Synthesis of (diarylmethyl)amines using Ni-catalyzed arylation of C(sp^3)-H bonds". J. Fernandez-Salas, E. Marelli, S. P. Nolan, *Chem. Sci.* **2015**, 4973–4977.

"Synthesis of an Intermediate of Nafoxidine via Nickel-Catalyzed Ketone Arylation". E. Marelli, J. A. Fernández Salas, S. P. Nolan, *Synthesis (Stuttg).* **2015**, *47*, 2032–2037.

"General and Mild Ni^0-Catalyzed α-Arylation of Ketones Using Aryl Chlorides". E. Marelli, J. A. Fernández-Salas, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Chem. – Eur. J.* **2015**, *21*, 3906–3909.

"Palladium-Catalyzed α-Arylation of Arylketones at Low Catalyst Loadings". E. Marelli, M. Corpet, S. R. Davies, S. P. Nolan, *Chem. – Eur. J.* **2014**, *20*, 17272–17276.

"Nickel-catalysed carboxylation of organoboronates". Y. Makida, E. Marelli, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2014**, *50*, 8010–8013.

Communication in conferences

"Ni-Catalysed Carboxylation of Organoboron Reagents". *USIC* 2, Glasgow, 5th Sep 2014 – Oral Presentation

"Ni-Catalysed Carboxylation of Organoboron Reagents". *CRITICAT Environment Day*, Harwell Catalysis Hub meeting, 22nd Jan 2015 – Oral Presentation

"Nickel catalysed deprotonative cross coupling reactions: a valuable alternative to palladium". *OMCOS* 18, 28th June to 2nd July 2015 – Poster Presentation

"Synthetic utility and mechanism of Nickel-catalysed deprotonative cross couplings". *Postgraduate Symposiums 2015*, St Andrews, 7th Dec 2015 – Oral Presentation

"Development of efficient and user friendly protocols for Palladium-catalysed carbonyl arylation". *Postgraduate Symposiums 2015*, St Andrews, 7th Dec 2016 – Oral Presentation

"Development of efficient and user friendly protocols for palladium-catalysed α-arylation of carbonyls". *Halogenase Network Meeting*, St Andrews, 17th Mar 2017 – Oral Presentation

Statement of collaborations

The scope of the reaction discussed in **Chapter 2** was studied in collaboration with Ms Sian R. Davies and Dr. Martin Corpet.

The methodology discussed in **Chapter 3** was developed in collaboration with Dr. Martin Corpet. The scope of the reaction was studied in collaboration with Mr Alessandro Bismuto, Ms Giulia Buccolini, Mr Massimiliano Curcio and Mr Rifahath Mon. The computational experiments were carried out by Yuri Minenkov (from the group of Luigi Cavallo).

The scope of the reaction discussed in **Chapter 4**, as well as its mechanism, were studied in collaboration with Dr. Josè A. Fernàndez-Sàlas. The X-Ray experiments were carried out by David B. Cordes.

The methodology discussed in **Chapter 5** was developed in collaboration with Dr. Josè A. Fernàndez-Sàlas.

The scope of the reaction discussed in **Chapter 6** was studied in collaboration with Mr Yohann Renault. Marfey's test was carried out in collaboration with Dr. Sunil V. Sharma.